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The 1986 U.S. EPA document Air Quality Criteria for Lead (EPA-600/8-83/028 aF-dF) evaluated in detail the latest scientific information concerning sources, routes, and levels of lead (Pb) exposure and associated health effects and potential risks. An Addendum (1986) to that document focuses on additional, newer studies concerning the effects of lead on cardiovascular function and on early physical and neurobehavioral development. The present Supplement to the above materials evaluates further still newer information emerging in the published literature concerning (1) lead effects on blood pressure and other cardiovascular endpoints and (2) the effects of lead exposure during pregnancy or early postnatally on birth outcomes and/or the neonatal physical and neuropsychological development of affected children. The evaluations contained in this Supplement and the 1986 Criteria Document and Addendum are to serve as scientific inputs to decisionmaking with regard to review and revision, as appropriate, of the National Ambient Air Quality Standards (NAAQS) for Lead.

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ABSTRACT

The 1986 U.S. EPA document Air Quality Criteria for Lead (EPA-600/8-83/028 aF-dF) evaluated in detail the latest scientific information concerning sources, routes, and levels of lead (Pb) exposure and associated health effects and potential risks. An Addendum (1986) to that document focuses on additional, newer studies concerning the effects of lead on cardiovascular function and on early physical and neurobehavioral development. The present Supplement to the above materials evaluates further still newer information emerging in the published literature concerning (1) lead effects on blood pressure and other cardiovascular endpoints and (2) the effects of lead exposure during pregnancy or early postnatally on birth outcomes and/or the neonatal physical and neuropsychological development of affected children. The evaluations contained in this Supplement and the 1986 Criteria Document and Addendum are to serve as scientific inputs to decisionmaking with regard to review and revision, as appropriate, of the National Ambient Air Quality Standards (NAAQS) for Lead.

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SUPPLEMENT TO THE 1986 EPA LEAD CRITERIA DOCUMENT ADDENDUM

I. INTRODUCTION

In the mid-1980's, the 1977 EPA criteria document, Air Quality Criteria for Lead (U.S. EPA, 1977) was updated and revised pursuant to Sections 108-109 of the Clean Air Act, as amended, 42 U.S.C. 7408 and 7409. The final version of the updated criteria document (U.S. EPA, 1986a) incorporating revisions made in response to public comments and CASAC review of earlier drafts, was completed in 1986 to be used as a basis for review and, as appropriate, revision of the National Ambient Air Quality Standard (NAAQS) for lead. An Addendum (U.S. EPA, 1986b) to the revised document, Air Quality Criteria for Lead (U.S. EPA, 1986a), was also completed in 1986 and evaluated newly published information concerning two topics: (1) the relationship between blood lead levels and cardiovascular effects; and (2) lead exposure effects on early development and stature.

In the three years since the 1986 Addendum was prepared, information pertaining to the health effects of lead has continued to emerge with regard to the topics addressed in that Addendum. Although newer findings have been generally consistent with the state of understanding that was articulated in the 1986 Addendum, they still need to be evaluated as part of an updated assessment of the latest scientific information that characterizes the health effects of lead (Pb) with clear relevance for decisionmaking on potential revision of the existing Lead NAAQS.

The present update focuses primarily on key findings that have emerged in the lead literature since 1986 in the areas of lead effects on: (1) blood pressure and related cardiovascular endpoints and (2) child development. It does not attempt to be comprehensive in reviewing this literature, nor does it attempt to address all the topics covered in the 1986 Air Quality Criteria Document and Addendum. Rather, its explicit purpose is to describe and interpret the critical effects of lead that have greatest significance for impending regulatory decisions regarding this environmental pollutant.

II. RELATIONSHIP OF BLOOD PRESSURE TO LEAD EXPOSURE

The 1986 Addendum (U.S. EPA, 1986b) addressed the issue of lead effects on the cardiovascular system in a review of the findings with regard to overtly lead-intoxicated individuals, epidemiologic studies of associations between lead exposure and increased blood pressure, toxicologic data providing evidence for lead-induced cardiovascular effects in animals, and information on the possible mechanisms of action of lead on cardiovascular function. The amount and sufficiency of the literature at that time were adequate to provide an initial evaluation of the topic, but did not come to a fully definitive consensus with regard to the contributory role of lead exposure to hypertension. Also not fully resolved was the extent to which lead-induced hypertension or other types of lead-induced pathogenic effects contribute to more serious morbidity (heart attack, stroke) and mortality of the human population.

For the purposes of this supplement, primary emphasis will be placed here on updated discussion of key human population-based studies which reflect primarily non-occupational exposure to lead. The largest study populations have been the second National Health and Nutrition Examination Survey (NHANES II) for the U.S. population (performed during the years 1976-80) and the British Regional Heart Study (BRHS), an ongoing evaluation of men aged 40 to 59 from 24 British towns. These studies were earlier described in detail in the published literature (Harlan et al., 1985; Pocock et al., 1984; Pirkle et al., 1985; Shaper et al., 1981); and further analyses of the subject data sets have been presented and discussed extensively at a 1987 U.S. EPA co-sponsored International Symposium on Lead-Blood Pressure Relationships and in other recent publications. In addition, analyses of several other data sets have been presented by other investigators at the 1987 Symposium or elsewhere in the published literature since the 1986 Addendum was prepared.

The 1986 Addendum (U.S. EPA, 1986b) noted that several then recently published studies provided generally consistent evidence for increased blood pressure (BP) being associated with elevated lead body burdens in adults, especially as indexed by blood lead (PbB) levels in various cohorts of adult men. None of the individual studies, it was noted, provided definitive evidence establishing causal relationships between lead exposure and increased blood pressure, but they collectively provided considerable qualitative evidence indicative of significant associations between blood lead and blood pressure levels. It was further emphasized that estimates of quantitative relationships between blood lead levels and blood pressure increases derived from such study results are subject to much uncertainty, given the relatively small sample sizes and limited population groups typically studied. On the other hand, the above-noted larger-scale studies (NHANES II and BRHS) of general population groups, were singled out as providing reasonably good bases for estimation of quantitative blood-lead blood-pressure relationships.

As reviewed in the 1986 Addendum (U.S. EPA, 1986b), in the BRHS, Pocock et al. (1984) evaluated relationships between blood lead concentrations, hypertension, and renal function indicators in a clinical survey of 7,735 middle-aged men (aged 40-49) from 24 British towns. Each man's blood pressure, while seated, was measured twice in succession by means of a London School of Hygiene sphygmomanometer. Diastolic pressure was recorded at phase V disappearance of sounds. The mean of the two readings of blood pressure was adjusted for observed variation within each town to correct for any differences among three observers. Results for 7,371 men included in data analyses indicated correlation coefficients of $r = +0.03$ and $r = +0.01$ for associations between systolic and diastolic blood pressure, respectively, and blood lead levels. The systolic blood pressure correlation, though small in magnitude, was nevertheless statistically significant at $p < 0.01$. However, analyses of covariance using data for men categorized according to blood lead concentrations only suggested increases in blood pressure at lower blood lead levels; no further significant increments in blood pressure were observed at higher blood lead levels either before or after adjustment for factors such as age, town, body mass index, alcohol consumption, social class, and observer. Evaluation of prevalence of hypertension defined as systolic blood pressure over 160 mm Hg revealed no significant overall trend; but of those men with blood lead levels over 37 µg/dl, a larger proportion (30 percent) had hypertension when compared with the proportion (21 percent) for all other men combined ($p = 0.08$). Similar results were obtained for diastolic hypertension defined as >100 mm Hg, i.e., a greater proportion (15 percent) of men with blood lead levels over 37 µg/dl had diastolic hypertension in comparison with the proportion (9 percent) for all other men ($p = 0.07$).

Pocock et al. (1984) interpreted their findings as being suggestive of increased hypertension at blood lead levels over 37 µg/dl, but not at lower concentrations typically found in British men. However, further analyses reported by Pocock et al. (1985) for the same data indicated highly statistically significant associations between both systolic ($p = 0.003$) and diastolic ($p < 0.001$) blood pressure and blood lead levels, when adjustments are made for variation due to site (town) in multiple regression analyses. The regression coefficients for log blood lead versus systolic and diastolic pressure were +2.089 and +1.809, respectively, when adjusted for town as well as body mass, age, alcohol, smoking, social class and observer. Noting the small magnitude of the association observed and the difficulty in adjusting for all potentially relevant confounders, Pocock et al (1985) cautioned at that time against prematurely concluding that elevated body lead burden has a causal influence on blood pressure.

The 1986 Addendum (U.S. EPA, 1986b) also noted that relationships between blood lead and blood pressure among American adults had begun to be evaluated in another large-scale study, as reported by Harlan et al. (1985), Pirkle et al. (1985), and Schwartz (1985a,b; 1986a,b). These analyses were based on evaluation of NHANES II data, which provide careful blood lead and blood pressure measurements on a large-scale sample representative of the U.S. population and considerable information on a wide variety of potentially confounding variables as well. As such, these analyses avoided the problem of selection bias, the healthy-worker effect, workplace exposures to other toxic agents, and problems with appropriate choice of control groups that often confounded or complicated earlier, occupational studies of blood-lead blood-pressure relationships. Three blood pressure readings were recorded for each subject: while seated early in the examination, supine midway in the examination, and seated near the end. First and fifth phase sounds were taken as systolic and diastolic pressures, respectively. The second seated blood pressure was used in statistical analyses, but analyses using the first seated pressure or a mean of the first and second seated pressure yielded similar results. Blood lead values, determined by AA spectrometry, were transformed to log values used in statistical analyses.

Relationships between blood pressure and other variables were evaluated in two ways. First, men and women were stratified into normotensive and hypertensive categories and mean values for relevant variables contrasted across the categories. For ages 21-55 yr, diastolic high blood pressure (≥ 90 mm Hg) male subjects ($N = 475$) had significantly ($p < 0.005$) higher PbB levels, body mass index values, and calcium foods than did normotensive male subjects

(N = 1,043). Similar results were obtained for aged 21-55 yr diastolic high blood pressure females (N = 263) in comparison to normotensive females (N = 1,316). For ages 56-74 yr subjects, significantly ($p < 0.05$) higher PbB levels were found for female subjects (but not males) defined as having isolated systolic high blood pressure (i.e., systolic ≥ 160 and diastolic < 90 mm Hg). Simple correlation analyses and step-wise multiple regression analyses were carried out as a second statistical evaluation approach; PbB values were entered into predictive models for systolic and diastolic pressure as well as several other pertinent variables (such as age, body mass index, etc.) entered sequentially according to greatest magnitude of variance explained for the dependent variable. The simple correlation analyses reported by Harlan et al. (1985) demonstrated statistically significant linear associations ($p < 0.001$) between blood lead concentrations and blood pressure (both systolic and diastolic) among males and females, aged 12 to 74 years. Using multiple regression analyses controlling for a number of other potentially confounding factors, however, the blood-lead blood-pressure associations remained significant for males but not for women after adjusting for the effects of other pertinent variables.

Additional analyses of NHANES II data reported by Pirkle et al. (1985) focussed on white males (aged 40 to 59 years) in order to avoid the effects of collinearity between blood pressure and blood lead concentrations evident at earlier ages and because of less extensive NHANES II data being available for non-whites. In the subgroup studied, Pirkle et al. (1985) found significant associations between blood lead and blood pressure even after including in multiple regression analyses all known factors previously established as being correlated with blood pressure. The relationship also held when tested against every dietary and serologic variable measured in the NHANES II study. Inclusion of both curvilinear transformations and interaction terms altered little the coefficients for blood pressure associations with lead (the strongest relationship was observed between the natural log of blood lead and the blood pressure measures). The regression coefficients for log blood lead versus systolic and diastolic blood pressure were 8.436 and 3.954, respectively. No evident threshold was found below which blood lead level was not significantly related to blood pressure across a range of 7 to 34 µg/dl. In fact, the dose-response relationships characterized by Pirkle et al. (1985) indicate that large initial increments in blood pressure occur at relatively low blood lead levels, followed by leveling off of blood pressure increments at higher blood lead levels. Pirkle et al. (1985) also found lead to be a significant predictor of diastolic blood pressure greater than or equal to 90 mmHg, the criterion blood pressure level now standardly employed in the United States to define hypertension. Additional analyses were performed by Pirkle et al. (1985) to estimate the likely public health implications of their findings concerning blood-lead, blood-pressure relationships. Changes in blood pressure that might result from a specified change in blood lead levels were first estimated. Then coefficients from the Pooling Project and Framingham studies (Pooling Project Research Group, 1978 and McGee and Gordon, 1976, respectively) of cardiovascular disease were used as bases: (1) to estimate the risk for incidence of serious cardiovascular events (myocardial infarction, stroke, or death) as a consequence of lead-induced blood pressure increases and (2) to predict the change in the number of serious outcomes as the result of a 37 percent decrease in blood lead levels for adult white males (aged 40-59 years) observed during the course of the NHANES II survey (1976-1980).

The earlier Addendum (U.S. EPA, 1986b) also noted that questions had been raised by Gartside (1985) and E.I. Du Pont de Nemours (1986) regarding the robustness of the findings derived from the analyses of NHANES II data discussed above and as to whether certain time trends in the NHANES II data set may have contributed to (or account for) the reported blood-lead blood-pressure relationships. Gartside reported analyses of HNANES II data which found that the size and level of statistical significance of coefficients obtained varied depending upon specific data aggregations used in analyzing the data. The largest and most significant coefficients for blood lead versus blood pressure were obtained by Gartside for data aggregated by age groups that approximated that of the 40-59 yr male aggregation described by Pirkle et al. (1985), with coefficients for most younger cohort groups aggregated by varying 20 yr age intervals (e.g., 21-40, 22-42 yrs, etc.) or older groups not always being significant at $p < 0.05$. As for the time trend issue, both blood lead and blood pressure declined substantially during the 4-yr NHANES II study and different geographic sites were sampled without revisitation of the same site over the survey period. Thus, variations in the sampling sites over time, coincident with changes in blood lead and/or blood pressure, might contribute to any observed associations between blood lead and blood pressure. E.I. Du Pont de Nemours (1986) reported that multiple regression coefficients decreased in magnitude and some became non-significant at $p < 0.05$ when geographic site was adjusted for in analyses of NHANES II data, including analyses for the male group (aged 12-74) reported on by Harlan et al. (1985) and for males (aged 40-59) reported on by Pirkle et al. (1985). For example, E.I. Du Pont de Nemours reported unpublished reanalyses of NHANES II data confirming significant associations for both aged 12-74 yrs males and 40-59 yr males between log PbB and systolic or diastolic blood pressure unadjusted for geographic site, but smaller coefficients (nonsignificant for diastolic) when geographic site was included in the analysis. However, neither the Gartside nor E.I. Du Pont de Nemours analyses adjusted for all of the variables that were selected for stepwise inclusion in the Harlan et al. (1985) and Pirkle et al. (1985) published analyses by means of *a priori* decision rules for inclusion of variables having significant associations with blood pressure. Also, other differences existed in regard to specific aspects of the modeling approaches employed, making it extremely difficult to assess clearly the potential impact of variation in selection of age groups and geographic site adjustment on NHANES II analyses results.

In order to address the "site" issue more definitively, Schwartz (1985a,b; 1986a,b) carried out a series of additional reanalyses of the NHANES II data. Those analyses confirm that the regression coefficients remain significant for both systolic and diastolic blood pressure when site is included as a variable in multiple regression analyses. Of several different approaches used by Schwartz, the most direct was holding all aspects of the original Pirkle et al. (1985) analyses the same except for the addition of a variable controlling for the 64 geographic sites sampled in NHANES II. Using this approach, the cofficients for log PbB in relation to either diastolic or systolic BP dropped somewhat from those of the original analyses when site was controlled for (i.e., from 8.44 to 5.09 for systolic and from 3.95 to 2.74 for diastolic blood pressure), but the coefficients for each still remained significant at $p < 0.05$. When still other approaches were used to control for site along with variations in other variables included in the analyses, statistically significant results were still consistently obtained both for males aged 40-59 and for males aged 20-74. The results obtained by Schwartz (1985a,b; 1986a,b) via reanalysis of NHANES II data (unadjusted versus adjusted for geographic site) are presented in Table 1 in comparison to results reported by E.I. Du Pont de Nemours (1986) and in relation to the findings presented by Pocock et al. (1984, 1985) for British men (also unadjusted versus adjusted for site).

TABLE 1. COEFFICIENTS FOR THE NATURAL LOG OF BLOOD LEAD CONCENTRATION (logPbB) VS. BLOOD PRESSURE (BP) IN MEN WITH AND WITHOUT ADJUSTMENT FOR SITE VARIABLES

Analysis Performed by	Study Group	Coefficient of log PbB vs. BP: Unadjusted for Site	Coefficient of log PbB vs. BP: Adjusted for Site
Pocock et al. (1984, 1985)	British Regional Heart Study White males aged 40-59		
	Systolic (n=7371)	1.68**	2.09**
	Diastolic (n=7371)	0.30	1.81***
Schwartz (1985a,b)	NHANES II Males aged 20-74		
	Systolic (n=2254)	5.23***	3.23**
	Diastolic (n=2248)	2.96***	1.39*
E.I. Du Pont de Nemours(1986)	NHANES II Males aged 12-74		
	Systolic (n=2794)	3.43***	1.95*
	Diastolic (n=2789)	2.02***	0.36
Schwartz (1986a,b)	NHANES II White males aged 40-59		
	Systolic (n=543)	8.44**	5.01*
	Diastolic (n=565)	3.95**	2.74*
E.I. Du Pont de Nemours (1986)	NHANES II White males aged 40-59		
	Systolic (n=553)	6.27**	3.46*
	Diastolic (n=575)	4.01**	1.93*

*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

The 1986 Addendum (U.S. EPA, 1986b) concluded that, overall, the analyses of data from the two large-scale general population studies (British Regional Heart Study and U.S. NHANES II Study) discussed above collectively provide highly convincing evidence demonstrating small but statistically significant associations between blood lead levels and increased blood pressure in adult men. The strongest associations appear to exist for males aged 40-59 and for systolic somewhat more so than for diastolic pressure. Virtually all of the analyses revealed positive associations for the 40-59 aged group, which remain or become significant (at $p < 0.05$) when adjustments are made for geographic site. Furthermore, the results of these large-scale studies were noted to be consistent with similar findings of statistically significant associations between blood lead levels and blood pressure increases as derived from other smaller-scale studies discussed in the Addendum, which also mainly found stronger associations for systolic pressure than for diastolic.

The Addendum (U.S. EPA, 1986b) further concluded that none of the observational studies in and of themselves can be stated as definitively establishing causal linkages between lead exposure and increased blood pressure of hypertension. However, the Addendum noted that the plausibility of the observed associations reflecting causal relationships between lead exposure and blood pressure increases is supported by: (1) the consistency of the significant associations found by numerous independent investigators for a variety of study populations; and (2) by extensive toxicological data discussed in the 1986 Addendum which clearly demonstrate increases in blood pressure for animal models under well-controlled experimental conditions. The precise mechanisms underlying relationships between lead exposure and increased blood pressure, the Addendum further stated, appear to be complex and mathematical models describing the relationships still remained to be more definitively characterized. At the time of the Addendum log PbB-BP models appeared to fit best the available data, but linear relationships between blood lead and blood pressure could not be ruled out. The most appropriate coefficients characterizing PbB-BP relationships also remained to be more precisely determined, although those listed in Table 1 obtained by analyses adjusting for site appeared to be the currently best available and most reasonable estimates of the likely strength of the association for adult men (i.e., generally in the range of 2.0-5.0 for log PbB versus systolic and 1.4 to 2.7 for log PbB versus diastolic blood pressure). The 1986 Addendum went on to note that the full range of blood lead levels that may be associated with increased blood pressure also remained to be more clearly defined. However, the collective evidence from the above studies points toward low or moderately elevated blood lead levels as being associated with blood pressure increases, with certain evidence (e.g., the NHANES II data analyses and some other study results) also indicating significant relationships between blood pressure elevations and blood lead levels ranging down, possibly, to as low as 7 µg/dl.

The earlier Addendum (U.S. EPA, 1986b) further stated that the quantification of likely consequent risks for serious cardiovascular outcomes, as attempted by Pirkle et al. (1985), also remained to be more precisely characterized. The specific magnitudes of risk obtained for serious cardiovascular outcomes in relation to lead exposure, estimated on the basis of lead-induced blood pressure increases, depend crucially upon: the form of the underlying relationship and size of the coefficients estimated for blood-lead blood-pressure associations; lead exposure levels at which significant elevations in blood pressure occur; and coefficients estimating relationships between blood pressure increases and specific more serious cardiovascular outcomes. It was noted that uncertainty still existed regarding the most appropriate model and blood-lead blood-pressure coefficients, which made it difficult to resolve which specific coefficients should be used in attempting to project more serious cardiovascular outcomes. Similarly, it was indicated that it is difficult to determine appropriate blood lead levels at which any selected coefficients might be appropriately applied in models predicting more serious cardiovascular outcomes. Lastly, it was noted that the selection of appropriate models and coefficients relating blood pressure increases to more serious outcomes is also fraught with uncertainty. Questions exist regarding the general applicability of coefficients derived from the Pooling Projects and Framingham Study to the men aged 40-59 in the general U.S. population. Further analyses of additional large scale epidemiologic data sets, it was stated in the Addendum, would be necessary to determine more precisely quantitative relationships between blood-lead and blood-pressure, and more serious cardiovascular outcomes as well.

The Addendum (U.S. EPA, 1986b) went on to note further that the above findings, while pointing toward a likely causal effect of lead in contributing to increased blood pressure need to be placed in broader perspective in relation to other factors involved in the etiology of hypertension. The underlying causes of increased blood pressure or "hypertension" (diastolic blood pressure above 90 mm Hg), which occurs in as many as 25 percent of Americans, are not yet fully delineated (Frohlich, 1983; Kaplan, 1983). However, it is very clear that many factors contribute to development of this disease, including hereditary traits, nutritional factors and environmental agents. The relative roles of various dietary and environmental factors in influencing blood pressure and the mechanisms by which they do so are a matter of intense investigative effort and debate (see proceedings of conference "Nutrition and Blood Pressure: Current Status of Dietary Factors and Hypertension," McCarron and Kotchen, 1983). The contribution of lead, compared to many other factors evaluated in various analyses discussed above, appears to be relatively small, usually not accounting for more than 1-2 percent of the variation explained by the models employed when other significant factors are controlled for in the analyses.

Many of the above issues and questions have been further addressed since the 1986 Addendum was completed, in part at the 1987 Lead-Blood Pressure Symposium and in other recent publications as well. Presentations and discussions at the 1987 Symposium (see Victery, 1988a) were contributed by (1) many of the key scientists who have carried out important investigations of the relationship of lead exposure and hypertension (including observational, epidemiologic, and experimental reports), as well as (2) other experts in hypertension and cardiovascular disease in general. Several speakers reviewed their analyses of the NHANES II data (Harlan, 1988; Schwartz, 1988; Gartside, 1988; Landis and Flegal, 1988) and the British study (Pocock et al., 1988). Elwood et al. (1988) also summarized the results of two new large-scale Welsh studies. Pocock further provided a new comparison of the relative magnitude of the contribution of lead exposure to blood pressure changes based on intercomparison of the results of the NHANES II, British, and Welsh studies. A number of other relevant papers were also presented which described studies of lead-blood pressure relationships in selected populations of nonoccupationally exposed individuals, as well as workers (Kromhout, 1988; Moreau et al., 1988; Weiss et al., 1988; Wedeen, 1988; Cooper, 1988; Selevan et al., 1988; de Kort and Zwennis, 1988; Elwood et al., 1988; Neri et al., 1988; Staessen et al., 1988; Sharp et al., 1988). Other presentations addressed pertinent toxicological findings from *in vivo* or *in vitro* animal studies (Vander, 1988; Chai and Webb, 1988; Kopp et al., 1988; Boscolo and Carmignani, 1988; Weiler et al., 1988; Victery, 1988b).

With regard to new findings reported at the Symposium, a further alternative analysis of the data from NHANES II (use of a generalized Mantel-Haenzel test) was reported by Landis and Flegal (1988). In order to more definitively assess the robustness of the earlier NHANES II results (Harlan et al. 1985; Pirkle et al., 1985; etc) and, also, to evaluate possible time-trend effects confounded by variations in sampling sites, Landis and Flegal (1988) carried out further analyses for NHANES II males, aged 12-74, using a randomization model-based approach to test the statistical significance of the partial correlation between blood lead and diastolic blood pressure, adjusting for age, body mass index, and the 64 NHANES II sampling sites. Simple linear and multiple regression coefficients between log PbB and diastolic BP for all males (aged 12-74) were 0.15 and 4.90, respectively; for various groups broken out by age (≤20, 21-39, ≥40 yrs) and body mass index levels, the respective coefficients ranged from 0.04 to 0.12 and from 1.29 to 3.55 (predominantly between 2.3 and 3.6), displaying considerable consistency across age-body mass comparison groups. Also, the most stringent or "conservative" approach used to calculate a randomized model statistic controlling for effects due to 64 sampling sites yielded a test statistic of 4.62 (still significant at $p < 0.05$). The authors noted that: (1) the association must be sufficiently robust to persist across 478 subgroups formed on the basis of factors also having an association with the levels of blood lead and blood pressure; and (2) nevertheless, even with the severe adjustments by sampling sites, age, and Quetelet index, the diastolic blood pressure/blood lead relationship remained statistically significant at the $p < 0.05$ level. In summary, their analyses indicate that the significant linear association between blood-lead levels and diastolic blood pressure readings cannot be dismissed as due to concurrent secular trends in the two variables across the 4-year survey period. Finally, the authors noted that, even though these partial correlations are not large, the magnitude of the regression coefficients suggests that elevated blood lead levels may be an important risk factor for elevated blood pressures, as developed in considerably greater detail for the restricted group of white men 40 to 59 years of age (as described in Pirkle et al., 1985).

Also reported on at the 1988 Symposium were two surveys in Wales which evaluated possible relationships between blood lead and blood pressure (Elwood et al., 1988a,b). The Welsh Heart Programme was carried out in 1985 throughout Wales, using a stratified cluster random sample of 21,000 households, with 2,010 male and female adult subjects being included in the survey population for whom blood lead determinations were made. Complete blood lead, blood pressure, and other key data were available for 865 men and 856 women. Mean blood lead values for men were 12.4 µg/dl and for women 9.6 µg/dl. Blood lead increased with age (1 µg/dl every 15.6 years in men and every 13.1 years in women). The partial regression coefficients with standard error were reported after the effect of age had been removed by cubic regression. In males, the coefficients for systolic and diastolic pressure were 0.82 ± 1.49 and 1.29 ± 0.95, respectively. For females, these coefficients were 0.19 ± 1.46 and 0.54 ± 1.00. In neither sex was the relationship statistically significant. Categorizing the data by blood lead increments demonstrated no trend in the blood pressure levels.

The second group studied was about half of the planned subjects in the Caerphilly Collaborative Heart Disease study; this study on ischemic heart disease was based on a cohort of men aged 45-59, living in Caerphilly, a small town in Wales. Several risk factors for ischemic heart disease were considered. Blood pressure was measured with a random-zero muddler sphygmomanometer after a 5-minute rest and during a cold pressor test. The correlation coefficients for resting systolic and diastolic pressure were 0.0183 and 0.0230, respectively, and for the rise in pressure with the cold pressor test, 0.0342 and 0.0078 respectively. None were significant at $p < 0.05$. Ranking the blood pressure readings according to blood lead groups did not reveal any trend in the percentage of subjects with systolic blood pressure greater than 160 mm Hg.

The authors (Elwood et al., 1988a,b) only corrected for age as the single confounding factor controlled for, because all other factors are positively correlated with both blood pressure and blood lead. They concluded that, in the event these other factors (e.g., cigarette use and alcohol consumption) were controlled for, they would probably reduce the already trivial (and nonsignificant) relationships found by them for blood lead and blood pressure measurements in the two Welsh studies.

At the 1988 Symposium, Pocock compared the results of the NHANES II data analyses as discussed by Schwartz (1988), his analyses of the British study (Pocock et al., 1988), and the two Welsh studies (Elwood et al., 1988a,b). Figure 1 shows the magnitudes of effects obtained for adult men in these four large-scale studies, relating systolic blood pressure to blood lead concentration, as depicted by Pocock et al. (1988). The graph shows each study's estimated change in mean systolic blood pressure for each doubling of blood lead (e.g., from 8 to 16 µg/dl), together with 95% confidence limits. Pocock concluded that an overview of data from these large epidemiological surveys provide reasonably consistent evidence on lead and blood pressure. That is, whereas the NHANES II data on 2,254 U.S. men indicate a slightly stronger association between blood lead and systolic blood pressure than Pocock's British study, the data from the two Welsh studies on over 2,000 men also showed a small positive, (but not statistically significant) association. Pocock noted that the overlaping confidence limits for all these studies suggest that there may be a weak positive statistical association whereby systolic blood pressure in adult men is increased by about 1 mm Hg for every doubling of blood lead concentration.

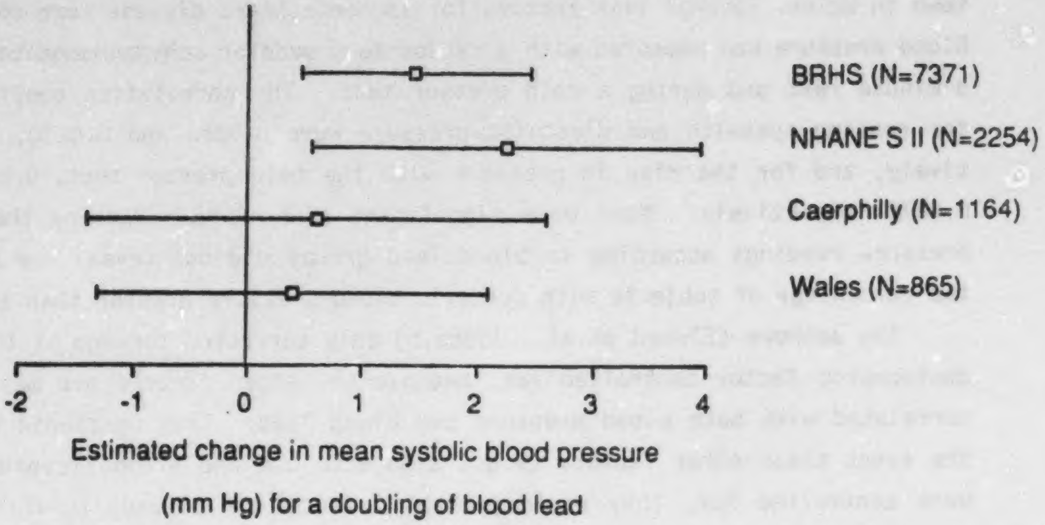

Figure 1. Comparison of study results from four larger-scale epidemiology studies of lead-blood pressure relationships in audlt men. BRHS = British Regional Heart Study analyses, described by Pocock et al. (1988); NHANES II = National Health and Nutrition Evaluation Survey analyses described by Schwartz (1988); Caerphilly and Wales = Welsh studies described by Elwood et al. (1988a,b).

Source: Pocock et al. (1988).

There was an additional report of an analysis of cross-sectional data from Canada (Neri et al., 1988) presented at the 1988 Lead-Blood Pressure Symposium. This study was performed on data collected during 10 months of 1978-1979 for 2,193 subjects aged 25 to 64. The zero-order correlation between diastolic blood pressure and blood lead level was found to be 0.115. The authors concluded that, although this association is a weak one (as was also the case in the NHANES II data), its statistical significance is not in doubt ($p < 0.001$). They further concluded that (1) the Canadian data were at least weakly supportive of the inference drawn from NHANES II, in that elevation of blood lead did seem to entail some risk of blood pressure elevation, but (2) it would be premature, in the absence of longitudinal data, to infer that this is a cause-and-effect relationship. Neri et al., 1988 then reported the findings for a group of subjects studied longitudinally for blood lead levels and blood pressure. That is, in a study of lead foundry workers, an association was found between short-term changes in an individual's blood lead level and contemporary changes in diastolic pressure, which remained significant after allowance for age (or time) trends and for effects attributable to changes in body weight. The authors also noted that short-term changes in urinary cadmium were similarly predictive of diastolic blood pressure levels.

There were several other reports presented at the 1988 Symposium with regard to smaller-scale observational studies of blood lead and blood pressure in two types of occupationally lead-exposed groups: bus drivers (Sharp et al., 1988) and policemen (Weiss et al., 1988 and Moreau et al., 1988). These studies all yielded findings that are also indicative of lead-induced increases in blood pressure.

In other recent reports besides those presented at the 1988 Symposium, three new studies (with generally small study cohorts) of occupationally exposed workers have yielded further results with regard to lead effects on blood pressure or other cardiovascular outcomes. For example, Parkinson et al. (1987) reported findings on data collected in 1982 from 270 lead workers and 158 nonexposed workers in Pennsylvania. Four measures of lead exposure were used: (a) employment at lead exposure vs. control plants; (b) current blood lead values at time of examination (exposed group mean = 39.9 µg/dl vs. 7.4 µg/dl for controls); (c) zinc protoporphyrin values at time of examination: (d) time weighted average (TWA) blood lead values for lead-exposed workers since date of hire. Other risk factors (age, years of education, etc.) were also included in the regression analysis. Of the three lead measures, only TWA blood lead was significantly, although modestly, correlated with blood pressure. After controlling for other predictive risk factors, including age, the effect of TWA on blood pressure was no longer significant and the authors did not find evidence of renal disease.

Also, in 1987, de Kort and colleagues reported finding a statistically significant increase in systolic and diastolic pressure in 53 exposed males compared with 52 controls (de Kort et al, 1987). Blood lead averaged 47.4 µg/dl vs. 8.1 for controls. Blood and urine cadmium were also higher than in controls; there were no adverse effects on kidney function. The prevalence of clinically-defined hypertension (systolic greater than 160 mm Hg and/or diastolic greater than 95 mm Hg and/or under treatment for hypertension) was higher in the exposed group, but the observed relative risk was not different.

In addition to the above study results which focussed primarily on lead-blood pressure effects in adult males, some additional analyses of such relationships in females have become available since the 1986 Addendum and the 1987 Lead-Blood Pressure Symposium. For example, Schwartz (1989) has recently reported the results of still further analyses of the NHANES II data set. These latest analyses used variables identified as being important in earlier NHANES II analyses and examined the relationship between blood lead and blood pressure in both males and females, aged 20-74 years. The analyses were carried out in stages, with separate regressions first being performed for males and females. Diastolic blood pressure was regressed on age, age^2, Quetelet's body mass index, and the natural log of blood lead. If, in this first step, lead was significant, then a stepwise regression was carried out taking into account a number of covariates or potentially confounding cofactors (e.g., dietary sodium, smoking, etc.); and final models were then ultimately estimated using SURREGR (a program correcting for study design effects as well). Statistically significant relationships were found between blood lead and blood pressure in both males ($p < 0.01$) and females ($p < 0.01$) in the first stage regressions, correcting for the above-noted covariates. Lead also continued to be significantly related to blood pressure in the separate stepwise regressions for males and females. The final models yielded a smaller, but statistically significant ($p < 0.03$) blood lead coefficient (1.640) for females than the coefficient for males (2.928; $p < 0.006$). These results therefore (1) further confirm the earlier findings of Schwartz and other investigators demonstrating significant associations between blood lead and blood pressure increases in adult males in the NHANES II study population and (2) demonstrate analogous, although somewhat smaller effects in women from the same study population.

In another study, Grandjean et al. (1989) evaluated lead-hypertension relationships in a cohort of 504 men and 548 women born in the same year and residing in the Glostrup area of Denmark. Both blood lead concentrations and blood pressure determinations were first obtained at age 40 and then, again, five years later for 451 men and 410 of the women. The average blood lead levels for men at age 40 and 45 years were 13 and 9 µg/dl, respectively; for women they were 9 and 6 µg/dl, respectively, at age 40 and 45 years. At age 40, women with systolic blood pressure above 140 mm Hg and/or diastolic above

90 mm Hg had slightly elevated blood leads compared to non-hypertensive women; but no differences were found for blood lead levels in men with increased versus normal (i.e., 140 or 90 mm Hg, respectively, for systolic and diastolic) blood pressure. Significant correlations were found between log blood lead and systolic blood pressure in both men and women and diastolic blood pressure in women only at age 40, but not at age 45. The relationship at aged 40 indicated a doubling of blood lead being associated with a ≤ 3 mm Hg increase in blood pressure. When blood hemoglobin and alcohol intake (the only two of nine potential confounders assessed that were significantly related to both blood lead and blood pressure) were entered into multiple regression analyses, then all blood-lead blood-pressure associations become non-significant. Grandjean et al. (1989) noted that the initial association found between blood lead and blood pressure was similar or slightly weaker than those earlier reported for the BRHS (Pocock et al., 1985) or the NHANES II (Pirkle et al., 1985) data analyses. The impact of alcohol and blood hemoglobin on the subsequent multiple regression outcomes indicate clear confounding with blood lead and an inability in this study to separate out relative contributions due to those factors versus lead (with blood lead increasing with number of units of alcohol consumed as documented in the study cohort at age 40, for example). The authors (Grandjean et al.) further noted that non-response and loss to follow-up, the very low range of blood lead values, and the limited statistical power of the study (with fewer than 1,000 subjects) to detect small effects may help to account for their observed pattern of results.

The issue of lead effects on more serious cardiovascular disease outcomes, possibly mediated by lead effects in blood pressure or via other lead-induced pathogenic processes has been further addressed since the 1986 Addendum to the EPA Lead Criteria Document was prepared. Some of the newer evidence has been derived from studies of occupationally exposed workers and other new results have emerged from still further analyses of the two larger-scale BRHS and NHANES II data sets.

The causes of mortality of lead workers in the United Kingdom between 1926 and 1985, for example, have recently been updated in a case-control study written by Fanning (1988). There were 867 deaths in men with relatively high occupational exposure to lead during these years, and 1206 deaths during the same period in men whose exposure had been low or absent. During the period between 1946 and 1965 there was a significant excess of deaths from cardiovascular disease; but there was no difference between the two groups over the past

20 years. Also, no statistically significant excess in the number of deaths from malignant neoplasms was evident. Fanning concluded that the previous evidence of an increased risk of death from cerebrovascular disease (in lead workers) was therefore confirmed, but it would seem that with the introduction of stricter standards of lead control this increased risk has now disappeared, as has any marginal risk of death from malignant disease.

Another occupational exposure study, an analysis of causes of death in U.S. battery and lead production workers during the years 1947 to 1980 was carried out, was presented at the 1987 Lead-Blood Pressure Symposium by Cooper (1988). Mortality causes were coded according to the seventh (1955) revision of the International Classification of Diseases. Data were from deaths of 4,519 battery plant workers and 2,300 lead production or smelter workers during this time period. Cooper reported that there were significant excess deaths for "other hypertensive disease" (444-447) and "chronic nphritis" (592-594); but deaths from other hypertension-related diseases did not show comparable excesses and renal cancer deaths were fewer than expected. Also, Selevan et al. (1988) reported at the 1987 Symposium that an analysis of causes of mortality in 1,281 lead smelter workers employed at an Idaho smelter between 1940 and 1965 did not suggest an association between occupational lead exposure and mortality from hypertension. On the other hand, the data do suggest an association between lead and renal disease and, possibly, renal cancer.

The 1988 Symposium report by Pocock et al. (1988) not only reviewed relationships between blood lead concentration and blood pressure as determined in the British Regional Heart Survey, but also looked at relationships between lead and more serious cardiovascular outcomes. The results of these further analyses of the BRHS data set were reported by Pocock et al. (1988) to show that, by 6 years of follow-up, 316 of the men had major ischemic heart disease and 66 had a stroke. After controlling for the confounding effects of cigarette smoking and town of residence, statistical analyses did not yield statistically significant associations between blood lead levels and such cardiovascular events. However, as the blood lead-blood pressure association is so weak, Pocock et al. (1988) noted, it is unlikely that any consequent association between lead and cardiovascular disease could be demonstrated from prospective epidemiological studies.

On the other hand, Schwartz (1989) has recently reported results derived from new NHANES II data analyses, which provide evidence for significant associations between blood lead levels and electrocardiogram (ECG) abnormalities indicative of left ventricular hypertrophy (LVH). Such ECG abnormalities represent an early indicator of cardiovascular disease that is much more common than frank myocardial infarctions. The logistic regression analyses employed by Schwartz (1989) yielded a small (0.028) but statistically significant ($p < 0.01$) coefficient for an association between blood lead levels and increased prevalence of LVH, taking into account age, race and sex (all of which were significantly related to LVH at $p < 0.01$, < 0.0001, and < 0.0001, respectively). The interaction terms for sex or race differences, however, were nonsignificant ($p > 0.20$) with regard to the cardiovascular effects of lead.

The Schwartz (1989) results are consistent with previous reports of cardiovascular effects being associated with high levels of lead exposure, e.g., Kirkby and Gyntelberg's 1985 report of a 20% increase ($p < 0.01$) in ischemic changes as coded on the Minnesota Codes in lead workers as compared to controls matched on age, race, and several other pertinent factors. The new findings by Schwartz, however, point toward small but not inconsequential increased risks for serious cardiovascular outcomes being associated with the relatively low range of blood lead levels encountered in the general U.S. adult population. It remains to be determined to what extent the observed lead effects on left ventricular hypertrophy or other cardiovascular functions are due to a lead-induced increase in blood pressure or to some other lead-related pathogenic mechanism.

At the 1988 Symposium, there was extensive discussion concerning controversy in the published epidemiology literature about the nature of a relationship between blood lead and blood pressure. As summarized by Tyroler (1988), the general population studies discussed above were seen as pointing toward a causal relationship between increases in blood-lead levels and significant and increases in blood pressure, extending to below values below those currently considered to be clinically significant as hypertensive. Tyroler further noted that the association has not been found in all studies and, when present, has been such that the increase in blood pressure with increase in blood lead levels has been of small absolute magnitude and not constant across age, sex, and race subgroups. Nevertheless, despite the seemingly small elevations in blood pressure when viewed from the clinical perspective of each individual, Tyroler further noted that the potential public health importance of a blood-lead blood-pressure relationship is considerable due to the strong association of blood pressure with cardiovascular morbidity and mortality, the leading cause(s) of death in our society, and the large number of individuals exposed.

Importantly for substantiating the plausibility of blood-lead blood-pressusre associations observed in human populations, the physiological and pharmacological regulation of blood pressure has been studied extensively by experimental investigators. Much of the then available information on the subject was discussed in the 1986 Addendum (U.S. EPA 1986b). It is now understood that various hormonal regulatory systems, vascular smooth muscle, and heart contractility all contribute to the development of blood pressure changes. Several of the speakers at the 1988 Symposium (Victery, 1988a) also reviewed findings of changes in the cardiovascular system in animals exposed to lead. For example, Victery (1988b) reviewed the experimental studies that have been conducted over 40 years on the effects of lead on blood pressure. Differences in animals species, age at beginning of exposure, level of lead exposure, and the effects of lead on blood pressure were described. It was noted that in several of the high-dose experiments, hypertension was observed, but nephrotoxicity of lead may have contributed to its development. In one experiment, high lead exposure may have reduced an elevated blood pressure. In contrast, lower dose experiments consistently demonstrated a hypertensive effect. The data suggest that a biphasic dose-response relationship may exist. Future research should be able to characterize in animals dose-response relationships for blood pressure effects across low-level lead exposure ranges most applicable to the general human population.

With regard to mechanisms potentially underlying lead-blood pressure relationships, Vander (1988) reviewed the chronic effects of lead on the renin-angiotensin system (one of the primary regulatory hormones for blood pressure). The changes observed in both animals and humans are highly variable and are dependent on the lead exposure level, the time of exposure, and other stimuli of the renin-angiotensin system. The human data are consistent with the tentative hypothesis that lead-exposed persons may have higher plasma renin activity (PRA) than normal during periods of modest exposure but normal or depressed PRA following more chronic severe exposures.

In another 1988 Symposium paper, the effects of lead on vascular reactivity were described by Chai and Webb (1988). There is convincing evidence that lead alters vascular reactivity in lead-exposed animals, which demonstrated a 15 to 20 mm Hg increase in systolic blood pressure. Increased pressor responsiveness to catecholamines has been demonstrated in an enhanced contraction of isolated vascular smooth muscle to adrenergic agonists. Further experimental evidence suggests that there are alterations in the mechanisms that regulate intracellular calcium concentration and that this may contribute to the abnormal vascular function in lead-induced hypertension. There were further reports of morphological, biochemical, and functional alterations in cardiovascular tissue in the reports by Kopp et al. (1988) and Boscolo and Carmignani (1988). The paper by Kopp et al. (1988) in the Symposium volume reviews the cardiovascular actions of lead, including evidence that lead exposure (at least at high levels) leads to morphological, biochemical, and functional derangements of the heart. The experimental literature also confirmed findings of cardiovascular complications in experimental animals. Findings include myocarditis, electrocardiographic disturbances, heightened catecholamine arrhymogenicity, altered myocardial contractile responsiveness to inotropic stimulation, dengerative structural and biochemical changes affecting the musculature of the heart and vasculature, hypertension, hyperchloesterolemia, atherosclerosis, and increased vascular reactivity to alpha-adrengergic agonists. The precise nature of the exposure-response relationships that apply are still poorly characterized, as well as the exact pathogenic mechanisms for the effects of lead on the cardiovascular system; but importantly, the experimental results provide clear evidence for lead causally affecting cardiovascular function.

In the 1987 Symposium discussion session (Victery et al., 1988), one of the invited discussants, Dr. Anthony Johns proposed a number of critical experiments to understand how lead may be affecting blood pressure and whether blood pressure changes can be reversed by removing lead from the diet. Inhibitors of the angiotensin-converting enzyme (now used as antihypertensive therapeutic agents) could be tried to determine if this can prevent the blood pressure increase during lead exposure. The levels of intracellular calcium should be measured in vascular tissue and the pharmacologic agents that block calcium or potassium channels in cell membranes should be examined to determine if they might reduce the effects of lead.

CONCLUSIONS

With regard to the effects of lead on blood pressure, the new information emerging since preparation of the 1986 Addendum, overall, substantiates further the main conclusions stated in that Addendum. Sufficient evidence exists from both the four large-scale general population studies discussed above (NHANES II, BRHS, and the two Welsh studies) and numerous other smaller-scale studies to conclude that a small but positive association exists between blood lead levels and increases in blood pressure. Quantitatively, the relationship appears to hold across a wide range of blood-lead values, extending possibly down to as low as 7 µg/dl for middle-aged men and, furthermore, an estimated mean increase of about 1.5-3.0 mm Hg in systolic blood pressure appears to occur for every doubling of blood lead concentration in adult males and something less than 1.0-2.0 mm Hg for adult females. The plausibility of these relationships observed in epidemiologic studies of human populations being of a causal nature is supported by controlled experimental animal studies demonstrating increased blood pressure effects clearly attributable to lead, with an apparent biphasic dose-response relationship being involved (i.e. blood pressure elevations at low lead dose levels and possible blood pressure reductions at very high lead exposure levels).

The implications of lead-induced blood-pressure increases with regard to potential increased risk for other, more serious cardiovascular outcomes still remain to be more clearly delineated. As noted by Tyroler and other discussants at the 1988 Symposium mentioned above, essentially any increase in blood pressure carries with it likely increased risk (albeit however small) for stroke, heart attack, and/or associated mortality. As such, projections of potential lead effects on such outcomes, as were modeled by Pirkle et al. (1985) and discussed in the 1986 Addendum, are not unreasonable in view of the potential very large public health impacts; however, much caution must be exercised in accepting the validity of any specific quantitative estimates derived from such projections in view of the uncertainties associated with selection of the specific coefficients used for (1) blood-lead blood-pressure relationships and (2) relationships between blood pressure increases and more serious cardiovascular outcomes. The difficulty in directly demonstrating associations between lead exposure and stroke, heart attacks, etc. lies in the very large study cohorts (many thousands of subjects) that would be necessary to have sufficient statistical power to detect the relatively small increased risk levels expected for the more serious cardiovascular outcomes. Some newly available results (i.e. those of Schwartz, 1989) from at least one large scale study help to illustrate the possibility of detecting indications of such small increased risks in the general population.

III. NEUROBEHAVIORAL AND GROWTH EFFECTS IN INFANTS AND CHILDREN

A major advance in the epidemiological investigation of the health effects of lead occurred with the advent of independent but somewhat coordinated prospective studies of child development. Some of the results of four such studies were discussed in the 1986 Addendum (U.S. EPA, 1986b). Much of the same information, with updating, was also presented in a critical review and interpretation by Davis and Svendsgaard (1987). The four prospective studies in question were conducted in Boston, Cincinnati, Cleveland, and Port Pirie, Australia.

Based on an assessment of these studies, the 1986 Addendum concluded that fetal lead exposure could have undesirable effects on infant mental development, length of gestation, and possibly other aspects of fetal development, with the most consistent evidence pertaining to neurobehavioral function. In particular, "All of these studies taken together suggest that neurobehavioral deficits, including declines in Bayley Mental Development Index scores and other assessments of neurobehavioral function, are associated with prenatal blood lead exposure levels on the order of 10 to 15 µg/dl and possibly even lower, as indexed by maternal or cord blood lead concentrations" (U.S. EPA, 1986b, p. A-48).

This update summarizes and assesses the evidence from these and other, more recent studies, both individually and collectively, and draws conclusions regarding their implications for regulatory decision-making.

Boston

As noted in the 1986 Addendum, a series of reports by Bellinger, Needleman, and their colleagues (Bellinger et al., 1984a, 1985, 1986a,b) described the results of a longitudinal study of early neurobehavioral development through the first two years of life in a cohort of Boston children. More recent updates on this work have since been published by Bellinger et al. (1987a, 1989a), covering the same period of development. The latter reports confirm that performance on the Bayley Mental Development Index (MDI) at 6, 12, 18, and 24 months postnatally is inversely related to cord blood lead levels at birth and that the amount of deficit in infants with cord blood lead levels of 10-25 µg/dl is 0.25-0.5 standard deviations, or approximately 4-8 points on the MDI (Table 2). Moreover, Bellinger et al. (1989a) found that this association

TABLE 2. INFANTS' MENTAL DEVELOPMENT INDEX SCORES ACCORDING TO CORD BLOOD LEAD GROUP

Cord Blood Lead Group	Mental Development Index Score			
	6 Months	12 Months	18 Months	24 Months
	Mean ± Standard Deviation			
Unadjusted score				
Low	109.2 ± 12.9	113.1 ± 12.5	113.4 ± 15.5	115.9 ± 17.2
Medium	108.6 ± 12.0	115.4 ± 12.9	116.6 ± 16.7	119.9 ± 14.4
High	106.1 ± 11.1	108.7 ± 12.8	109.5 ± 17.5	110.6 ± 16.5
	Mean ± Standard Error			
Controlled for potential confounders*				
Low	110.2 ± 1.3	114.7 ± 1.6	116.2 ± 1.9	118.9 ± 1.8
Medium	108.0 ± 1.3	114.4 ± 1.5	114.8 ± 1.9	117.8 ± 1.7
High	105.9 ± 1.4	108.9 ± 1.6	109.5 ± 2.0	111.1 ± 1.8
p value**	0.095	0.020	0.049	0.006
No. of infants	201	199	187	182

*Least-squares mean ± standard error, derived from regression equations that included 12 potential confounders and cord blood lead group coded as two indicator variables.

**Indicates p value associated with the F ratio that evaluates whether the mean Mental Development Index for any cord blood lead group differed significantly from the common mean after potential confounders were controlled for.

Source: Bellinger et al. (1987a).

was evident in several different regression models and was not an artifact of the approach they used in analyzing the data. In addition, more detailed analyses showed that the average MDI deficit in high cord lead infants (blood lead levels of 10-25 µg/dl) was not due to a disproportionate influence of results from infants at higher (e.g., >15 µg/dl) blood lead levels. That is, the MDI effect was evident across the entire range of blood lead levels starting at 10 µg/dl, which reinforces the previous selection of 10-15 µg/dl as a blood lead level of concern for early developmental deficits (U.S. EPA, 1986b).

Other recent analyses by Bellinger et al. (1988) have focused on the interaction of lead-related Bayley MDI deficits with socioeconomic status (SES). Even in the relatively advantaged cohort of the Boston study, infants from other than the highest SES grouping tended to have lower covariate-adjusted scores on the MDI. Moreover, the second-year MDI performance of these "lower" SES children was adversely affected at lower blood lead levels than was the performance of the higher SES children. Specifically, within the lower SES grouping, infants with mid-range cord blood lead levels of 6-7 µg/dl scored significantly worse on the Bayley MDI than infants with low cord blood lead levels of <3 µg/dl.

Bellinger et al. (1987b, 1989b) have also recently reported preliminary results of later testing of 170 children of the Boston cohort at about 5 years (57 months) of age on the McCarthy Scales of Children's Abilities. They found that the association between cord blood lead and cognitive performance, as measured by the General Cognitive Index (GCI) of the McCarthy Scales, was no longer statistically significant at 57 months. However, the relationship between blood lead level at 24 months postnatally and GCI scores was statistically significant, even after adjusting for covariates and confounders (Table 3). The mean 24-month blood lead level was 6.8 µg/dl (SD = 6.3). Other postnatal blood lead measurements at 18 and 57 months were consistent with this association but failed to achieve statistical significance. The size of the deficit amounted to approximately 3 GCI points for every natural log unit increment in blood lead level.

Bellinger et al. (1989b) examined the change in cognitive performance of children from 24 to 57 months of age in relation to pre- and postnatal lead exposure levels and various sociodemographic variables. Improvement in relative performance was associated with lower blood lead levels at 57 months, higher SES, higher HOME scores, higher maternal IQ, and female gender. Conversely, the risk of an early deficit persisting to 5 years of age was increased in children with higher prenatal lead exposure (10-25 µg/dl) and either high postnatal exposure or less favorable sociodemographic factors. For example, "if two children with high cord blood lead achieved the same MDI score at 24 months, but one had a low blood lead level [<3 µg/dl] at 57 months while the other had a high [>10 µg/dl] level, the child with lower exposure would be expected to have a GCI score that is 0.61 standard normal deviate units higher..., [which] corresponds to a difference of 9.8 points" (Bellinger et al., 1989b). Similar comparisons of males and females with high cord blood lead levels indicated that boys scored 7.7 points lower than girls on the GCI, and children in the lower SES grouping scored 13.3 points lower than those in the higher SES grouping.

TABLE 3. CHANGE IN McCARTHY GENERAL COGNITIVE INDEX (GCI) AND SUBSCALE SCORES ASSOCIATED WITH EACH NATURAL LOG UNIT INCREASE IN BLOOD LEAD LEVEL

Age at Measurement of Blood Lead Level (months)	GCI	Verbal	Perceptual-Performance	Quantitative	Memory	Motor
6	0.28 ± 1.29* .83**	0.75 ± 0.93 .42	-0.72 ± 0.77 .35	0.00 ± 0.76 .99	0.82 ± 0.83 .33	0.02 ± 0.81 .98
12	-1.43 ± 1.25 .25	-0.98 ± 0.89 .27	-0.64 ± 0.79 .42	-0.09 ± 0.74 .90	-0.09 ± 0.81 .91	-0.82 ± 0.80 .31
18	-1.62 ± 1.39 .25	-0.19 ± 1.01 .85	-0.72 ± 0.87 .41	-1.20 ± 0.82 .15	-0.52 ± 0.91 .57	0.30 ± 0.89 .74
24	-2.95 ± 1.42 .040	-0.41 ± 1.04 .69	-2.58 ± 0.88 .004	-1.45 ± 0.85 .088	-0.66 ± 0.94 .49	-0.90 ± 0.92 .33
57	-2.28 ± 1.88 .23	-1.06 ± 1.38 .44	-2.33 ± 1.13 .042	0.13 ± 1.13 .91	0.49 ± 1.25 .70	-1.89 ± 1.15 .10

*Parameter estimate ± standard error.

**p-value associated with the null hypothesis that the parameter estimate is zero.

Source: Bellinger et al. (1987b).

Bellinger et al. (1987b) also evaluated the degree of disparity in McCarthy subscale performance, since learning disabilities are often highly specific to certain cognitive functions. A greater number of subscale discrepancies was associated with higher (>10 μg/dl) concurrent (57 month) blood lead levels.

Cincinnati

Interim results of a longitudinal study of inner-city children born in Cincinnati, Ohio were reported by Dietrich et al. (1986, 1987a) and summarized in the 1986 Addendum. Structural equation modeling, a statistical method of examining relationships among factors that may be both independent and dependent variables or mediators of effects, indicated that prenatal lead exposure had an indirect effect on 6-month MDI and PDI (Psychomotor Development Index) scores through its effects on gestational age and/or birth weight. Higher prenatal (maternal) blood lead levels were associated with reduced gestational age and reduced birth weight, which in turn were significantly associated with reduced MDI and PDI performance.

Although the Cincinnati subjects were not grouped by blood lead levels for these analyses, separate analyses of birth weight effects by Bornschein et al. (1989) investigated the dose-response relationship by grouping into five 6-μg/dl intervals. An increase in the percentage of low birthweight newborns between the 7-12 μg/dl grouping and the ≥13 μg/dl grouping implied the possibility of a threshold for low birthweight effects (categorically defined as less than 2750 g) in the vicinity of 12-13 μg/dl, although a precise determination is not possible and could extend as low as 7 μg/dl or perhaps as high as 18 μg/dl. To the extent that low birthweight mediated the effect of lead on Bayley scores in the Cincinnati study, the inferred information is consistent with the conclusion (U.S. EPA, 1986b) that a blood lead level of 10-15 μg/dl, and possibly lower, constitutes a level of concern for impaired performance on the Bayley MDI.

Dietrich et al. (1987b, 1989a,b) later reported more complete results for neurobehavioral developmental outcomes in approximately 300 infants from the Cincinnati study (Table 4). The children were tested on the Bayley Scales at 3, 6, 12, and 24 months of age. After adjusting for covariates, deficits in 3- and 6-month Bayley MDI scores were significantly associated with prenatal (maternal) and cord blood lead levels, confirming the earlier, preliminary

TABLE 4. RESULTS OF MULTIPLE REGRESSION ANALYSES EXAMINING THE RELATIONSHIP BETWEEN BLOOD LEAD LEVEL AND PERFORMANCE ON THE BAYLEY MENTAL INDEX AT 3-24 MONTHS OF AGE*

Blood Lead Measure (μg/dl)	N	Beta	Standard Error	t Value	p Value**
3-month MDI					
Prenatal	228	-.34	0.17	-1.96	.05
Umbilical cord	80	-.60	0.26	-2.30	.02
10 day	261	.06	0.22	0.26	.79
3 month	n.r.	-.23	0.18	-1.30	.20
6-month MDI					
Prenatal	249	-0.89	0.34	-2.60	0.009
Prenatal by Child Sex		1.53	0.51	2.98	0.003
10 day	283	-3.15	1.30	-2.43	0.016
10 day by SES		0.16	0.08	2.13	0.034
12-month MDI					
Prenatal	258	0.09	0.26	n.r.	N.S.
Umbilical cord	98	-0.17	0.36	n.r.	N.S.
10 day	257	-0.62	0.31	n.r.	<0.04
24-month MDI					
Prenatal	237	0.51	0.22	2.31	0.022
10 day	270	-0.02	0.25	-0.07	0.948
3 month	270	0.24	0.21	1.12	0.262
Maximum 1st Year	270	0.24	0.10	1.39	0.166
Maximum 2nd Year	270	0.10	0.07	1.39	0.166
24 months	270	0.13	0.09	1.45	0.149

*Betas adjusted for different sets of covariates for each age of MDI testing.

**Two-tailed values.

Sources: Dietrich et al. (1987b, 1988, 1989b).

analyses of Dietrich et al. (1987a). The magnitude of the deficit in the 3-month MDI amounted to 6 points for every 10-μg/dl increment in cord blood lead; the corresponding 6-month MDI deficit was nearly 7 points. Also, a conservative reanalysis (Dietrich et al., 1989b) of the 6-month data using all potential covariates and confounders confirmed earlier findings, although interactive effects with gender and SES were evident (see below). However, neither prenatal nor cord blood lead measures were significantly related to 12-month MDI scores, although the association between neonatal (10-day) blood lead levels and 12-month (as well as 6-month) MDI scores remained statistically significant (Dietrich et al., 1989a). It should be noted that analyses of the 12-month data are not yet final.

By 24 months, no statistically significant negative relationships were detectable between lead exposure variables (either pre- or postnatal) and MDI scores (Dietrich et al., 1989b). Only one parameter estimate (for prenatal blood lead) achieved statistical significance ($p = 0.0217$), and it was positive rather than negative.

In addition, the Bayley Infant Behavior Record (IBR) was administered at 12 and 24 months to assess the infants' social and emotional development (Dietrich et al., 1989a,b). Factor analysis of the 30 IBR items at 24 months yielded principal factors of Sustained Attention, Activity Level, and Positive Mood, which were used in regression analyses to assess the effect of lead exposure. Lower scores on Sustained Attention and Positive Mood factors were both significantly associated with increased neonatal (10-day) blood lead levels, consistent with the 12-month MDI relationship to neonatal blood lead (Dietrich et al., 1989a). However, none of the 24-month IBR results achieved statistical significance. Bayley PDI results were incomplete.

Dietrich et al. (1987b, 1989b) also found that gender and SES interacted with the lead exposure-MDI relationship. Male infants and children from the lower half of the SES distribution for this cohort were more sensitive to the effects of early lead exposure on neurobehavioral development. For example, male infants showed an 8.67-point deficit on the 6-month MDI for every 10-μg/dl increment in prenatal blood lead, and infants below the sample median SES score had a 7.57-point deficit for every 10-μg/dl increment in neonatal blood lead (Dietrich et al., 1989b).

Dietrich et al. (1989b) interpreted their failure to detect a persistent effect of fetal lead exposure on the 24-month Bayley Scales as probably due to a neurobehavioral catch-up response, similar to that observed in infant twins (Wilson, 1986) or other infants compromised during prenatal development (Tanner, 1981). Exploratory analyses indicated that the greatest percentage increase in MDI raw scores (number of items passed) from age 3 months to 24 months was inversely related to prenatal lead exposure, birth weight, gestation, and head circumference (Dietrich et al., 1989b). Thus, those infants with the highest prenatal blood lead levels, lowest birth weight, shortest gestation, or smallest head circumference showed the greatest degree of catch-up in postnatal neurobehavioral development.

As previously noted, the Cincinnati study has also produced evidence of direct effects of prenatal lead exposure on infant physical development at birth. Bornschein et al. (1989) reported that initial results from 202 infants showed an inverse relationship between maternal blood lead levels and both birth weight and length. Maternal blood lead samples were obtained at the first prenatal visit (between 6 and 28 weeks of gestation; mean = 16 wks). The mean maternal blood lead level was 7.6 µg/dl (range: 1-26 µg/dl). Exclusion criteria included birth weight less than 1500 g, less than 35 weeks gestational age at birth, twin birth, and serious medical conditions. Regression analyses considered 21 potential confounders and covariates. The final regression model for birth weight showed that log maternal blood lead was significantly related to birth weight, but interacted with maternal age to produce a significant ($p < 0.007$) reduction in covariate-adjusted birth weight. Thus, the effect of each natural log increment in blood lead varied from a birthweight reduction of 58.1 g for 18-year-old mothers to a reduction of 600.1 g for 30-year-old mothers. Maternal blood lead and race interacted to produce a significant reduction in birth length in white infants ($p < 0.025$). Thus, the birth length of white infants decreased ~2.5 cm for each natural log increment in maternal blood lead. Maternal blood lead showed no significant relationship to covariate-adjusted head circumference or gestation length. Obstetrical complications and Apgar scores also showed no relationship with lower birth weight or lead exposure.

Separate analyses of 861 women (including the 202 subjects just described) from the Cincinnati cohort, but including pregnancies of not less than 20 weeks duration, also showed a highly significant ($p < 0.0006$) negative relationship between maternal blood lead level and covariate-adjusted birth weight (Bornschein et al., 1989). Overall, this cohort had a decrease of approximately 114 g in birth weight for each natural log increment in maternal blood lead.

Analyses of postnatal growth rates in a cohort of 260 children from the Cincinnati study suggested an interactive effect of prenatal and postnatal lead exposure (Shukla et al., 1987). Splitting prenatal blood lead levels and the average increase in postnatal blood lead levels at the median (7.7 µg/dl for prenatal, 3.4 µg/dl for the postnatal increase) provided a matrix of low/low, low/high, high/low, and high/high exposure conditions. Analysis of data for 129 subjects in the high prenatal exposure classification indicated that covariate-adjusted growth rates for stature over 3-15 months of age were significantly ($p = 0.006$) and negatively related to the postnatal increase in blood lead level. No effect was seen for the low prenatal exposure group. Thus, for infants whose prenatal blood lead levels were greater than 7.7 µg/dl, there would be, on average, a 2-cm difference in height at 15 months of age between those infants who experienced no increase in postnatal blood lead and those who experienced an increase of ~10 µg/dl.

Other recent results of a neurobehavioral nature from the Cincinnati study have also been reported by Bhattacharya et al. (1988, 1989). Postural sway was assessed by an automated apparatus in 33 children at 6 years of age (Bhattacharya et al., 1988). Initial results indicated that maximum blood lead level during the second year of life was significantly related to degree of postural sway or imbalance at 6 years. Blood lead levels in this sample peaked during the second year, averaging 25.6 µg/dl (range: 9.3-49.4 µg/dl), measured quarterly. The later report by Bhattacharya et al. (1989) covers 63 children and confirms the earlier results showing a significant relationship between sway and second year maximum blood lead ($r = 0.34$, $p = 0.02$). Although more test results are needed to fully explore these effects, these preliminary findings provide additional indications of neurobehavioral disruption during early childhood exposure to lead.

Cleveland

As noted in the 1986 Addendum (U.S. EPA, 1986b), the prospective study conducted by Ernhart and her colleagues has provided some direct as well as indirect evidence of an effect of prenatal lead exposure on neurobehavioral development. Ernhart et al. (1985a, 1986) reported significant associations between cord blood lead levels and measures of Abnormal Reflexes (on the Brazelton Neonatal Behavioral Assessment Scale: NBAS) and Neurological Soft Signs (on the Graham-Rosenblith Behavioral Examination for Newborns: G-R).

Also, the G-R Muscle Tonus measure was significantly related to maternal blood lead levels at delivery. However, restricting the analyses to only 132 pairs of mother-infant data, Ernhart et al. found only the G-R Neurological Soft Signs to be significantly related to cord blood lead. A brief report on later outcomes in this same cohort mentioned a significant association between performance on the G-R Neurological Soft Signs scale and 12-month MDI scores (Wolf et al., 1985). Thus, it is possible to infer a relationship between cord blood lead levels and 12-month MDI performance in the Cincinnati study, although Ernhart et al. (1985a, 1986) did not conclude that such an association exists. Since the mean cord blood lead was 5.89 µg/dl and the maximum was only 14.7 µg/dl, any effect of prenatal lead exposure necessarily occurred at blood lead levels below 15 µg/dl.

Later reports by Ernhart and her colleagues (Ernhart et al., 1987a, 1988; Ernhart and Morrow-Tlucak, 1989) presented more complete results from their continuing longitudinal study (Table 5). The Bayley MDI was administered at 6, 12, and 24 months; the Bayley PDI and the Kent Infant Development Scale (KID) at 6 months; and the Stanford-Binet IQ test at 36 months. Postnatal blood lead levels were measured at 6, 24, and 36 months. A total of 285 children from the original cohort of 389 were sampled for blood lead levels; N's for individual analyses ranged from 109 to 165. After control for covariates, maternal blood lead accounted for a significant amount of the variance in 6-month MDI, PDI, and KID scores. Although these three relationships were all negative (higher PbB associated with lower developmental scores), concurrent blood lead was positively related to the 6-month KID and accounted for nearly as much variance as did maternal blood lead. Maternal blood lead levels averaged 6.50 µg/dl, with a maximum of 11.8 µg/dl; 6-month blood lead levels averaged 10.05 µg/dl, with a maximum of 24.00 µg/dl.

More recent results from testing these children at age 4 years, 10 months on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) were reported by Ernhart et al. (1987b). Analyses were based on N's ranging from 117 to 211. Although bivariate correlations were statistically significant for all PbB-WPPSI relationships except 6-month PbB, in no case did PbB account for a significant amount of the variance (by two-tailed t test) after control for 13 covariates (Table 6).

TABLE 5A. THE RELATIONSHIP OF FETAL (MATERNAL AND CORD) PbB WITH LATER DEVELOPMENTAL OUTCOMES

					Incremental Regression Model			
					PbB With Covariate Control		Race by PbB Interactions	
Blood Lead Measure	Developmental Measure	N	r	Covariate Variance	Variance	t	Variance	t
Maternal	6 Month MDI	127	-.24**	0.2460	0.0302	-2.12*	0.0161	-1.57
	6 Month PDI	127	-.21*	0.2485	0.0295	-2.12*	0.0093	-1.19
	6 Month KID	119	-.28**	0.1464	0.0779	-3.22***	0.0182	-1.56
	1 Year MDI	145	-.14	0.1887	0.0002	-0.16	0.0026	-0.64
	2 Year MDI	142	-.14	0.3664	0.0020	+0.48	0.0000	-0.01
	3 Year S-B IQ	138	-.10	0.3894	0.0059	+1.09	0.0020	-0.63
Cord	6 Month MDI	113	-.14	0.2394	0.0046	-0.76	0.0056	-0.74
	6 Month PDI	113	-.11	0.1891	0.0006	-0.26	0.0249	+1.73
	6 Month KID	109	-.10	0.1418	0.0107	-1.07	0.0051	+0.74
	1 Year MDI	127	-.24**	0.2327	0.0146	-1.47	0.0143	-1.46
	2 Year MDI	125	-.15	0.3746	0.0003	-0.21	0.0002	-0.13
	3 Year S-B IQ	120	-.21*	0.4393	0.0125	-1.54	0.0086	-1.28

*p <0.05, **p <0.01, ***p = 0.002, two-tailed tests.

TABLE 5B. THE RELATIONSHIP OF PRIOR AND CURRENT POSTNATAL PbB LEVELS WITH LATER DEVELOPMENTAL OUTCOMES

					Incremental Regression Model					
			Simple Correlation							
Blood Lead Measure	Developmental Measure	N	r	p*	Covariates	p	PbB with Covariate Control	p	Interaction	p
6 month	6 month MDI	146	-.09	.29	.18	.000	.01	.31	.01	.34
	6 month PDI	146	.06	.49	.19	.000	.01	.32	.00	.48
	1 year MDI	131	.08	.40	.14	.02	.01	.25	.00	.51
	2 year MDI	126	-.03	.74	.30	.000	.00	.95	.00	.63
	3 year S-B IQ	126	-.04	.65	.29	.000	.00	.49	.00	.87
2 year	2 year MDI	165	-.25	.000	.32	.000	.00	.95	.01	.07
	3 year S-B IQ	153	-.31	.000	.31	.000	.01	.29	.00	.32
3 year	3 year S-B IQ	167	-.27	.000	.36	.000	.00	.98	.01	.08

*Two-tailed statistical test.

Source: Ernhart et al. (1987a, 1988).

TABLE 6. THE RELATIONSHIP OF PRENATAL AND POSTNATAL LOG BLOOD LEAD WITH IQ AT AGE FOUR YEARS, TEN MONTHS

Blood Lead Measure	N	IQ[a]					
		Full Scale		Verbal Scale		Performance Scale	
		r[b]	t	r	t	r	t
Prenatal							
Maternal	134	-.23**	-0.27	-.25**	-0.49	-.23**	-0.48
Cord	117	-.21*	-0.54	-.22*	-0.78	-.20*	-0.78
Postnatal							
6 Months	121	-.06	-0.08	-.07	-0.26	-.08	+0.10
2 Years	149	-.38**	-0.69	-.36**	-1.41	-.34**	+0.22
3 Years	154	-.32**	+0.30	-.39**	-1.58	-.30**	+0.96
Mean	211	-.26**	+0.48	-.30**	-1.00	-.26**	+0.56

[a] WPPSI scores except for two S-B IQ scores; latter two cases were necessarily excluded from the tests of the Verbal and Performance Scales.

[b] r describes the unadjusted relationship of the PbB and IQ measures; t is the test of the increment in variance associated with the addition of PbB to the covariate variance in the IQ model.

*p <.05, **p <.01, two-tailed tests.

Source: Ernhart et al. (1987b).

Language development in the Cleveland cohort was also assessed at age 1, 2, and 3 years (Morrow-Tlucak and Ernhart, 1987). The Sequenced Inventory of Communication Development (SICD) was administered to assess expressive and receptive language development. In addition, productive speech (quantity, length of utterance, vocabulary, communicative intent, and intelligibility) was assessed at about 2 years. The number of subjects for each of the analyses was not reported, but the number of blood lead measurements over the period from delivery to 3 years ranged from 146 to 169. Alpha was set at 0.01. Several bivariate correlations achieved statistical significance, but no relationship achieved significance in multivariate F tests, although the regression analysis for cord PbB and mean length of utterance was significant at $p = 0.03$. By backward elimination, lead (cord PbB) remained in the model (at $p \leq 0.05$) for two measures of language development: mean length of utterance and one aspect of communicative intent ("expanded repetitions"). However, concurrent (2-year) blood lead was positively related to one aspect of intelligibility (a decrease in "unintelligible utterances").

Preliminary analyses of physical growth in the preschool period (up to 4 years, 10 months) revealed no significant negative relationship between either cord blood lead or integrated postnatal blood lead and height or weight in an unspecified number of children from the Cleveland study (Marler and Ernhart, 1987). Earlier analyses (Ernhart et al., 1986) of birth weight, length, and head circumference had shown no significant effect of either maternal blood lead (N = 185) or cord blood lead (N = 162).

Port Pirie

Vimpani et al. (1985) reported preliminary neurobehavioral results for the prospective study conducted in Port Pirie, South Australia. The Bayley MDI and PDI were administered to 592 children at age 24 months. Initial results indicated that a decline in 24-month MDI performance was significantly associated with postnatal blood lead levels at 6 months or integrated over the 24 months after birth. Although several covariates were taken into account in these partial linear regression analyses, maternal IQ had been measured for only part of the cohort and HOME scores had not yet been included in the analyses. Nevertheless, as noted in the 1986 Addendum, the available information suggested that results from the Port Pirie study were consistent with the other prospective studies in pointing to deficits on the Bayley MDI as a function of perinatal lead exposure.

Although postnatal rather than prenatal lead exposure appeared to play a greater role in the MDI deficits of the Port Pirie cohort, it has been noted that blood lead levels increased considerably after birth, particularly from 6 to 15 months of age, and that earlier testing on the Bayley Scales (e.g., at 6 months) might have revealed a more significant relationship with a measure of prenatal lead exposure (U.S. EPA, 1986b; Davis and Svendsgaard, 1987). Indeed, the Port Pirie investigators have since stated that "the likely greater impact of the much higher levels of PbB encountered postnatally" may have accounted in part for the difference in their results versus the other prospective studies (Wigg et al., 1988).

Later reports from the Port Pirie study have noted that the effect of postnatal blood lead levels on the 2-year MDI was attenuated as more complete control for maternal IQ and HOME scores was incorporated into the analysis, although all regression coefficients for postnatal blood lead measures remained negative (Vimpani et al., 1989; Wigg et al., 1988; Baghurst et al., 1987).

Elevations in 6-month blood lead continued to have the greatest measurable impact on 2-year MDI scores, although the regression coefficient for 6-month blood lead was only -0.16, with $p = 0.07$, after controlling for at least 15 covariates. The results indicated that "with other factors remaining constant, a child's MDI at 24 months will be 1.6 points (equivalent to 1.5%) lower for every 10 µg/dl rise in PbB at 6 months of age. .... Moreover, in view of the fit of a linear model in multiple regression analysis, these findings provide no evidence of a threshold effect" (Wigg et al., 1988).

Continuing study of the Port Pirie cohort has yielded results for neurobehavioral development at age four years (McMichael et al., 1988). The McCarthy Scales of Children's Abilities were administered to 537 children within 6 months of their fourth birthday; N's for individual analyses ranged from 463 to 534. Multiple regression analyses incorporating 18 covariates indicated that scores on the McCarthy GCI were significantly related to log-transformed postnatal blood lead levels at 6, 24, and 36 months as well as an integrated average for the four-year postnatal period (Table 7). Similar effects were also evident for the McCarthy Perceptual-Performance and Memory Scales.

The largest single coefficient (-15.0; $p = 0.04$) was for the GCI and integrated postnatal average blood lead relationship, which indicates that GCI scores decreased by 15 points for every 10-fold increment in blood lead. Alternatively stated, GCI scores declined approximately 7.2 points as blood lead levels increased from 10 to 30 µg/dl. Further analyses indicated that the relationship between lead exposure and GCI was as strong or even stronger at blood lead levels below 25 µg/dl than it was overall (geometric mean blood lead level peaked at 2 years: 21.2 µg/dl; integrated postnatal average: 19 µg/dl). Other analyses revealed no indication that GCI performance at four years was especially influenced by more recent blood lead levels; rather, the effect of lead on the GCI appeared to be cumulative across the entire postnatal period.

Pregnancy outcomes were also evaluated in the Port Pirie cohort (McMichael et al., 1986). A significantly elevated risk of preterm (<37 weeks) delivery was associated with maternal blood lead levels above 14 µg/dl. Neither birth weight nor spontaneous abortions (<20 weeks) showed a signficant association with blood lead levels. However, blood lead levels of mothers who had stillbirths were significantly lower than those who had live births (7.9 vs. 10.4 µg/dl). As discussed in the 1986 Addendum and by Davis and Svendsgaard

TABLE 7. ESTIMATED COEFFICIENTS OF LOG BLOOD LEAD CONCENTRATION FROM SIMPLE AND MULTIPLE REGRESSION ANALYSES OF McCARTHY SCORES AT THE AGE OF FOUR YEARS*

Blood Sample	General Cognitive Index Simple	 Partial	Perceptual-Performance Scale Simple	 Partial	Memory Scale Simple	 Partial
Prenatal average	-15.1 ± 4.7 (0.001)	-1.8 ± 5.7 (0.75)	-9.5 ± 2.7 (<0.001)	-4.1 ± 3.3 (0.22)	-4.8 ± 2.7 (0.07)	2.0 ± 3.3 (0.54)
Delivery	-10.4 ± 3.9 (0.008)	-0.4 ± 4.5 (0.93)	-5.1 ± 2.3 (0.03)	0.2 ± 2.7 (0.95)	-4.9 ± 2.2 (0.03)	-0.4 ± 2.6 (0.89)
Cord	-6.1 ± 3.4 (0.08)	3.3 ± 4.1 (0.42)	-3.0 ± 2.0 (0.13)	1.6 ± 2.4 (0.50)	-3.0 ± 2.0 (0.12)	2.6 ± 2.5 (0.27)
6 Month	-15.1 ± 3.8 (<0.001)	-8.5 ± 4.4 (0.05)	-7.8 ± 2.2 (<0.001)	-4.8 ± 2.5 (0.06)	-4.9 ± 2.2 (0.03)	-2.4 ± 2.5 (0.34)
15 Month	-14.3 ± 3.8 (<0.001)	-3.5 ± 4.8 (0.46)	-8.2 ± 2.2 (<0.001)	-3.2 ± 2.8 (0.26)	-5.3 ± 2.2 (0.01)	-0.5 ± 2.7 (0.87)
24 Month	-25.8 ± 4.3 (<0.001)	-11.1 ± 5.4 (0.04)	-13.5 ± 2.5 (<0.001)	-6.2 ± 3.2 (0.05)	-13.4 ± 2.4 (<0.001)	-7.3 ± 3.1 (0.02)
36 Month	-25.1 ± 4.3 (<0.001)	-13.1 ± 5.6 (0.02)	-13.6 ± 2.5 (<0.001)	-7.7 ± 3.3 (0.02)	-12.7 ± 2.4 (<0.001)	-[illegible].2 ± 3.2 (0.27)
48 Month	-20.1 ± 4.1 (<0.001)	-5.5 ± 5.1 (0.29)	-11.2 ± 2.4 (<0.001)	-4.0 ± 3.0 (0.18)	-10.3 ± 2.3 (<0.001)	-4.1 ± 3.0 (0.17)
Integrated postnatal average	-28.9 ± 5.5 (<0.001)	-15.0 ± 7.3 (0.04)	-15.1 ± 3.2 (<0.001)	-8.3 ± 4.1 (0.05)	-13.3 ± 3.1 (<0.001)	-7.9 ± 4.2 (0.06)

*The partial regression coefficients are from analyses incorporating 18 covariates. The p values are for assessments of the two-sided hypothesis that the estimates are not zero.

Source: McMichael et al. (1988).

(1987), this seemingly paradoxical relationship might reflect increased transfer of lead from the mother to the fetus, resulting in greater fetal toxicity and stillbirth. Vimpani et al. (1989) reported preliminary results of an analysis of tissue lead concentrations in cord and placental membrane and body that are consistent with this hypothesis. Placental membrane and body concentrations of lead were higher in cases of late fetal deaths and preterm births than for normal births. However, the number of cases analyzed was limited (e.g., 6 stillbirths, 23 preterm births) and statistical analyses have not been completed.

Sydney

Reports have recently started to emerge from a longitudinal study of children in Sydney, Australia (Cooney et al., 1989a, 1989b; McBride et al., 1989). Of an original cohort of 318, 298 mothers and infants were sampled for blood lead levels at birth. After 3 years, 215 children remained in the study. A second cohort of 123 children was also recruited because of "concern over the possible contamination of some of the early capillary blood samples" (Cooney et al., 1989b). However, the results reported by Cooney et al. (1989a) apparently pertain to the original cohort only. Geometric mean blood lead levels for mothers and infants at birth were 9.1 and 8.1 µg/dl, respectively (overall range: 0-29 µg/dl). Although blood lead measures were also taken at 6, 12, 18, 24, 30, and 36 months (McBride et al., 1989), the postnatal values were not considered in the analysis of neurobehavioral outcomes during the first three years. The Bayley MDI and PDI were administered at 6, 12, and 24 months, and the McCarthy GCI and Motor Scales were administered at 36 months. Other outcomes were also evaluated but the results have not yet been reported.

Unadjusted bivariate correlations between blood lead levels (either maternal or cord) and cognitive and psychomotor outcomes (either Bayley or McCarthy Scales) were generally small, positive, and nonsignificant (Table 8). The only statistically significant simple correlations were for the relationship between cord blood lead and the 12-month Bayley MDI ($r = 0.153$, $p < 0.05$, two-tailed) and PDI ($r = 0.167$, $p < 0.05$, two-tailed). However, the direction of the relationship was positive, i.e., as blood lead increased, Bayley scores increased. After adjustment for covariates, the contribution of blood lead to the variance in the regression model approached significance only for the

TABLE 8. REGRESSION OF DEVELOPMENTAL INDICES ON MATERNAL AND CORD BLOOD LEAD LEVELS

	Simple Correlations		Effect of Covariates			Incremental Effect of Lead		
Age	Maternal	Cord	R^2	F	p	R^2	F	p
6 Months								
Cognitive	-.044	-.061	.136	3.16	<.001	.008	1.22	>.25
Psychomotor	.035	.025	.153	3.63	>.001	.003	0.46	>.60
				df = 13,261			df = 2,259	
12 Months								
Cognitive	.015	.153*	.177	4.08	<.001	.008	1.17	>.30
Psychomotor	.081	.167*	.106	2.23	<.01	.019	2.60	.08
				df = 13,245			df = 2,243	
24 Months								
Cognitive	.006	.053	.219	4.79	>.001	.001	.19	>.70
Psychomotor	.021	-.060	.081	1.49	>.10	.013	1.54	>.20
				df = 13,222			df = 2,220	
36 Months								
Cognitive	.040	.045	.165	3.11	<.001	.001	.13	>.70
Psychomotor	.015	.010	.081	1.39	>.10	.001	.10	>.90
				df = 13,204			df = 2,202	

*p <.05, two-tailed test.

Source: Cooney et al. (1989a).

positive relationship between cord blood lead and 12-month Bayley PDI ($p = 0.08$, two-tailed).

Regression analyses and path models indicated that the greatest influences on MDI and PDI scores at 6 and 12 months were gestational age and HOME scores, while at later ages HOME and parental characteristics (maternal IQ and education) were the more important influences on cognitive measures. The fact that Bayley scores accounted for a significant amount of the variance in regressing HOME scores on prior HOME scores in two instances (12-month PDI for the 12- versus 6-month HOME and 36-month MDI for the 36- versus 24-month HOME) raises the question of whether lead exposure (e.g., maternal blood lead) might have covaried with HOME scores. This particular relationship was apparently not examined by the investigators. However, the authors did examine the relationships between maternal/cord blood lead and gestational age, which were shown to be statistically nonsignificant (as were also birth weight, obstetrical complication, and postnatal risk factors).

Cooney et al. (1989b) reported the results of testing the Sydney cohort at 4 years of age on the McCarthy GCI and Motor Scales. At 4 years, 207 children of the original cohort remained in the study. In addition to maternal and cord blood lead samples at delivery, postnatal blood lead samples were taken every 6 months. Geometric means for capillary and venous blood samples combined rose from 15 µg/dl at 6 months to a peak average of 16.4 µg/dl at 18 months and then declined to 10.1 µg/dl at 48 months.

Bivariate and partial (correcting for venous versus capillary collection) correlations between 48-month McCarthy Scales and blood lead levels at different ages were generally quite small, mixed in sign, and uniformly nonsignificant. Analyses using composite blood lead measurements (averaged over 12-month periods) produced only one significant relationship, a positive correlation ($r = 0.160$; $p < 0.05$, two-tailed) between first year blood lead and GCI performance (Table 9). However, after allowing for covariates, regression analysis showed the relationship to be only marginally significant ($p < 0.07$). Analysis of covariance did not indicate that change in developmental outcome from 36 to 48 months was significantly related to either current (48 month) or cumulative (current and prior) past lead exposure, although cumulative lead was a better predictor ($p = 0.14$) than current lead exposure alone ($p = 0.36$) for GCI scores. HOME score was stated to be the most important covariate for the GCI, apart from the 36-month GCI.

TABLE 9. REGRESSION OF DEVELOPMENTAL INDICES AT 48 MONTHS ON CURRENT AND PRIOR BLOOD LEVELS

		Unadjusted			Adjusted	
Age	ΔR^2	df	p	ΔR^2	df	p
Prenatal:						
Cognitive	.004	2,204	.36	.009	2,199	.14
Motor	.001	2,204	.91	.002	2,199	.55
First Year:						
Cognitive	.023	1,205	.03	.013	1,199	.07
Motor	.003	1,205	.46	.001	1,199	.67
Second Year:						
Cognitive	.001	1,205	.82	.002	1,199	.60
Motor	.001	1,205	.60	.004	1,199	.33
Third Year:						
Cognitive	.001	1,205	.70	.003	1,199	.76
Motor	.008	1,205	.20	.006	1,199	.26
Fourth Year:						
Cognitive	.001	1,205	.88	.001	1,199	.76
Motor	.005	1,205	.32	.001	1,199	.96
All Prior and Current:						
Cognitive	.044	6,200	.17	.028	6,193	.14
Motor	.022	6,200	.72	.018	6,193	.56

Source: Cooney et al. (1989b).

Mexico City

Preliminary results of a pilot study in Mexico City for a longitudinal investigation of developmental outcomes related to lead exposure and other factors have been reported by Rothenberg et al. (1989). Approximately 50 mothers were sampled for blood lead levels at 36 weeks (M36) of pregnancy and delivery (MD); umbilical cord blood lead (UC) was also sampled at delivery. Mean blood lead levels were: M36, 15.0 µg/dl; MD, 15.4 µg/dl; and UC, 13.8 µg/dl. The Brazelton Neonatal Behavioral Assessment Scale (NBAS) was administered to the infants at 48 hours and 15 and 30 days after birth.

The data were analyzed by calculating the trend of the NBAS subscale scores over the first 30 days by linear regression analysis and by computing the difference in M36 and MD values or M36 and UC values. The relationships among the various primary and secondary measures were then examined through bivariate correlations and multivariate regression analyses (Table 10). Significant bivariate correlations were found between UC blood lead and the 30-day trend in NBAS Abnormal Reflexes ($r = 0.299$, $p < 0.05$), between the M36-MD blood lead difference and Regulation of States ($r = 0.378$, $p < 0.05$), and between the MD-UC blood lead difference and Abnormal Reflexes ($r = -0.451$, $p < 0.01$). The signs of all the correlations reflected impairment of function. Stepwise multiple regression modeling with all covariates entered before the lead variable revealed that the blood lead differentials for M36-MD and for MD-UC accounted for a significant amount of the variance in the Abnormal Reflexes trend ($p \cong 0.03$ for each). Similarly, M36-MD accounted for a significant amount of the variance in Regulation of States ($p = 0.025$). However, UC alone was no longer significantly associated with Abnormal Reflexes.

Alternatively stated, these results reflect impaired neurobehavioral outcomes in infants as the mothers' blood lead levels increased from 36 weeks to delivery or as the infants' blood lead levels approached or exceeded the mothers' at delivery. Davis and Svendsgaard (1987) commented on the possible significance of such disequilibria in the normal maternal-fetal blood lead relationship and the possibility that the fetus/infant could act as a sink for the mother's lead burden. However, Rothenberg et al. (1989) speculated that some fetal stress factor may be responsible for both the disparity in fetal/infant lead burden and the unfavorable neurobehavioral outcomes in the neonate (cf. Ernhart et al., 1986).

Rothenberg et al. (1989) also evaluated physical development outcomes at birth in their cohort. After controlling for covariates, multiple regression analyses indicated that M36-MD and M36-UC each accounted for a significant amount of the variance in birthweight ($p < 0.05$); M36-UC accounted for a significant amount of the variance in chest circumference ($p = 0.054$); and UC and M36-UC accounted for a significant amount of the variance in trunk length ($p \cong 0.06$).

Yugoslavia

A longitudinal study involving two communities in Yugoslavia, Titova Mitrovica and Pristina, has been undertaken by Graziano et al. (1989a,b). T. Mitrovica is a major lead smelter and industrial site, whereas Pristina, 40 km to the south, serves as a relatively non-exposed control community. The analyses completed thus far have been retrospective as well as prospective. Only reproductive outcomes have been assessed.

TABLE 10A. SIGNIFICANT BIVARIATE CORRELATIONS OF 30-DAY NBAS* TREND AND LEAD MEASURES

Maternal lead at 36 weeks (M36)	---
Maternal lead at delivery (MD)	---
Umbilical cord lead (UC)	reflexes, 0.299**
M36 - MD	regulation of states, 0.378**
M36 - UC	---
MD - UC	reflexes, -0.451***

*NBAS = Neonatal Behavioral Assessment Scale.

**p <0.05.

***p <0.01.

TABLE 10B. EFFECT OF ADDITION OF LEAD TO THE STEPWISE MULTIPLE REGRESSION MODEL USING PRIOR ENTRY OF ALL CONTROL VARIABLES THAT HAVE SIGNIFICANT BIVARIATE CORRELATIONS WITH 30-DAY TREND OF NBAS*

NBAS Scale	Lead Measure	N	F Value	Additional Percent of Variance Explained by Lead	p Value
Reflex	M36 - MD	44	4.87	6.0	0.034
	MD - UC	44	5.08	6.2	0.030
Regulation of States	M36 - MD	44	5.54	8.5	0.025

*NBAS habituation scale not tested because of low number of subjects with complete data. All other variables not shown were not significant.

Source: Rothenberg et al. (1989).

Of the first 1032 women enrolled in the study, 639 (304 in T. Mitrovica; 335 in Pristina) had had at least one pregnancy (only first pregnancies were considered in the analysis) and had lived at their current address at least since their first pregnancy. Geometric mean blood lead levels at the time of initial interview were 15.9 µg/dl in T. Mitrovica and 5.1 µg/dl in Pristina. The rate of spontaneous abortions (fetal loss prior to 7th month) was not significantly different in the two communities: 16.4% of T. Mitrovica women versus 14.0% of Pristina women reporting such loss. Graziano et al. (1989b) noted that they had systematically attempted to demonstrate an association between lead exposure and spontaneous abortion and that their failure to detect such an association suggested that it did not exist at the levels of exposure encountered in their samples.

A preliminary analysis of prospective data from 907 births (401 in T. Mitrovica; 506 in Pristina) indicated that mean birthweights did not differ significantly between the two communities: 3308 g (SD = 566) in T. Mitrovica versus 3361 g (SD = 525) in Pristina. Geometric mean blood lead levels were 17.1 µg/dl in the former and 5.1 µg/dl in the latter mothers. Regression analysis controlling for several covariates also failed to show any significant relationship between mid-pregnancy blood lead levels and birthweight.

Glasgow

Following a cross-sectional duplicate diet study that showed, among other things, an inverse relationship between gestational age and lead exposure during pregnancy (Moore et al., 1982a), Moore et al. (1982b) initiated a prospective study of the neurobehavioral effects of lead in children born in Glasgow, Scotland. A major source of lead exposure for this population was its plumbosolvent drinking water. However, subsequent to a successful program to control the plumbsolvency of the water supply for Glasgow, average blood lead levels declined substantially (Richards and Moore, 1984). Notwithstanding this complication in the design of their prospective investigation, Moore et al. (1989) undertook to assess whether prenatal or perinatal lead exposure was associated with birth outcomes or postnatal neurobehavioral development.

Their study sample consisted of 151 subjects drawn from an initial pool of 885 families. Based on maternal blood lead levels during pregnancy, three groups, matched for social class, were created: high (≥30 µg/dl, mean = 33.05), medium (15-25 µg/dl, mean = 17.73), and low (≤10 µg/dl, mean = 7.02).

Infant blood lead levels were measured at 1 and 2 years of age, but were not included in the reported analyses because of incomplete records.

Although birth weight appeared to be inversely related to maternal blood lead (a reduction of nearly 100 g for each increment in blood lead grouping), no statistical analysis of the data was reported. Birth length showed a slight trend in the oppposite direction, and other pediatric measures (head circumference, Apgar scores, obstetric complications) showed no evident trend in either direction.

Unadjusted Bayley scores (MDI, PDI, and mean) at 1 and 2 years generally decreased with increasing maternal blood lead grouping. However, stepwise linear regression anlayses indicated that birth weight, social class, and HOME scores accounted for Bayley Scales performance better than lead exposure (as represented by maternal blood lead, water lead concentration, or reported history of pica). Since birth weight was significantly related inversely to lead exposure, it was removed from the model to see if the explanatory power of one of the lead variables could be improved. Only second year pica showed a notable improvement, although HOME score alone still had less predictive ability for 2-year Bayley scores than pica coupled with HOME score. An analysis of the Bayley IBR revealed no consistent direction of association between lead exposure and IBR factors. Moore et al. (1989) concluded that their dataset provided "no firm evidence for either a direct or an indirect contribution of lead to decrements in cognitive development."

Christchurch

Fergusson and his colleagues (Fergusson and Purchase, 1987; Fergusson et al., 1988a,b,c) collected shed deciduous teeth from more than 1000 children in Christchurch, New Zealand to assess their long-term lead exposure and the relationship of such exposure to neurobehavioral outcomes. Blood lead levels were not measured.

As reported by Fergusson et al. (1988b), IQ, reading ability, and school performance were assessed in relation to dentine lead levels in samples of 664-886 children from an original cohort of 1265 drawn from the Christchurch Child Development Study. The subjects were evaluated at ages 8 and 9 years on the WISC-R, the Burt Reading Test, and by teachers' ratings of reading, written expression, spelling, mathematics, and handwriting. All bivariate correlations between these outcomes and dentine lead levels were in the predicted direction (negative), and all but one (out of 18) were statistically significant at $p < 0.05$ (one-tailed). After correcting for test unreliability, dentine lead measurement error, sample selection factors, and several covariates, the coefficients for the reading test and all five teacher ratings at both ages 8 and 9 years remained significant. Further correction for pica (to test for the reverse causality hypothesis that reduced cognitive ability results in more pica, which in turn results in greater lead exposure) reduced the size of the correlations even more (ranging from -0.07 to -0.14), but 7/12 of the correlations remained statistically significant at $p < 0.05$ (Table 11).

TABLE 11. UNEXPLAINED CORRELATIONS BETWEEN DENTINE LEAD LEVELS (log μg/g) TAKING INTO ACCOUNT TEST RELIABILITY, CONFOUNDING COVARIATES, SAMPLE SELECTION FACTORS, AND REVERSE CAUSALITY VIA PICA

Measure	8 years r	8 years p*	9 years r	9 years p*
Verbal IQ	-0.03	N.S.	-0.02	N.S.
Performance IQ	-0.02	N.S.	-0.02	N.S.
Total IQ	-0.04	N.S.	-0.03	N.S.
Burt reading test	-0.07	<0.05	-0.08	<0.05
Teacher ratings				
Reading	-0.13	<0.001	-0.08	<0.10
Written expression	-0.13	<0.001	-0.08	N.S.
Spelling	-0.14	<0.001	-0.09	<0.10
Mathematics	-0.08	<0.10	-0.10	<0.05
Handwriting	-0.12	<0.05	-0.08	<0.10

*One-tailed test.

Source: Fergusson et al. (1988b).

Fergusson et al. (1988c) also investigated the hypothesis that the demonstrated relationship between lead exposure and school performance was due to lead-related deficits in attentional processes. Mothers' and teachers' ratings of signs of restless activity and inattention at ages 8 and 9 years were correlated with dentine lead levels of 888 children (Table 12). Several aspects of the ratings were significantly correlated with dentine lead, with bivariate correlations for total rating scores ranging between 0.08 ($p < 0.05$) and 0.14 ($p < 0.01$, one-tailed). Teachers' ratings were more highly correlated with lead and were also judged to be a more accurate measure of the children's behavior than were maternal ratings. After correcting for measurement errors,

TABLE 12. PRODUCT MOMENT CORRELATIONS BETWEEN MATERNAL, TEACHER BEHAVIOUR RATINGS AND DENTINE LEAD VALUES (log μg/g)

	8 years		9 years	
Measure	r	p*	r	p*
Maternal ratings				
Activity				
Restless, overactive	0.07	<0.05	0.05	<0.10
Excitable, impulsive	0.07	<0.05	0.05	<0.10
Constantly fidgeting	0.03	N.S.	0.04	N.S.
Always climbing	0.07	<0.05	0.04	N.S.
Squirmy, fidgety	0.03	N.S.	0.06	<0.05
Attention				
Short attention span	0.09	<0.01	0.08	<0.01
Inattentive, easily distracted	0.09	<0.01	0.05	<0.10
Can't settle to tasks	0.06	<0.05	0.04	N.S.
Total Score	0.11	<0.01	0.08	<0.05
Teacher ratings				
Activity				
Restless, overactive	0.09	<0.01	0.11	<0.001
Excitable, impulsive	0.03	N.S.	0.10	<0.001
Squirmy, fidgety	0.11	<0.001	0.13	<0.001
Very restless	0.10	<0.001	0.13	<0.001
Attention				
Inattentive, easily distracted	0.16	<0.001	0.14	<0.001
Short attention span	0.11	<0.001	0.12	<0.001
Poor concentration	0.13	<0.001	0.12	<0.001
Total Score	0.13	<0.001	0.14	<0.001

*One-tailed test.

Source: Fergusson et al. (1988c).

sample selection factors, covariates, and pica, the correlation between dentine lead and inattention/restless behavior was 0.08 ($p < 0.01$) at both 8 and 9 years of age.

Although small, the corrected correlations between dentine lead and various outcomes reflecting school behavior and performance were consistent and stable over a one-year interval in the Christchurch study. The uniformity and stability of these results across time provide compelling reason to judge the effects as real. However, this same study provided no evidence that intelligence, as measured by the WISC-R at 8 or 9 years of age, was related to dentine lead levels.

The lack of blood lead measurements makes it difficult to interpret the Christchurch study for dose-response information. However, the mean dentine lead value in this study was 6 μg/g, which may be compared to a mean dentine lead level of ~14.5 μg/g found by Needleman et al. (1979; see also Bellinger et al., 1984b) for a sample of 2335 Boston children. Given the comparability of the methods employed by Fergusson (Fergusson and Purchase, 1987; Fergusson et al., 1988a,b,c) and by Needleman et al. (1979), and an estimated mean blood lead level on the order of 30 μg/dl at age 2-3 years in the study by Needleman et al. (1979), it is possible to infer that the average blood lead level of the Christchurch cohort could have been roughly on the order of ≤15 μg/dl at age 2-3 years. Although this estimate is rather imprecise and based on several assumptions, it suggests that the level of lead exposure in the Christchurch study population was roughly comparable to populations in some of the other studies under consideration here.

Nordenham

As noted in the 1986 Addendum, Winneke et al. (1985a,b) enrolled 114 children in 1982 from a population of 383 children born 6-7 years previously in Nordenham, Federal Republic of Germany. An ongoing federal screening program of the Nordenham residents had taken blood samples from mothers and cords at delivery. The maternal geometric mean blood lead level was 9.3 μg/dl (range: 4-31); for umbilical cord, it was 8.2 μg/dl (range: 4-30). When tested at age 6-7, the children's average blood lead level was again 8.2 μg/dl, but distributed differently (range: 4-23). In terms of accounting for a significant amount of variance in various measures of reaction time performance, maternal blood lead was better than cord; the combination of maternal and cord blood lead was better than either alone; and the combination was about as good as concurrent blood lead. These relative standings are probably only rough comparisons, since differences in the quality of the samples from different sources and at different times could have affected these results (Winneke et al., 1985a).

Retesting of 76 of the Nordenham children at age 9, with blood lead levels then averaging 7.8 μg/dl (range: 4-21), indicated some persisting deficits in reaction time test performance related to blood lead levels 3 years earlier

(Winneke et al., 1989a,b). WISC-R performance was also significantly related to the preceding blood lead levels after correction for confounding. Concurrent blood lead did not significantly account for either reaction time or WISC-R performance at age 9, although it had (for reaction time errors) at age 6-7. No results were reported for the relationship of 9-year outcomes to perinatal blood lead measures.

Buffalo

A prospective study was recently initiated in the Buffalo, NY area by Shucard et al. (1988a,b). Cord blood levels averaged ~4.4 µg/dl for 802 newborns. Outcomes have not yet been reported.

Other Recent Studies

In addition to the longitudinal studies discussed above, several other studies of neurobehavioral function in lead-exposed children have been reported since the 1986 Addendum. Although most appear to be well conducted, many of these studies are of somewhat limited relevance, either because of their cross-sectional design, their relatively high blood lead levels, or their primary reliance on tooth lead as an exposure indicator. Despite its limitations, blood lead is currently the bioindicator of greatest utility for regulatory decision-making purposes. Consequently, the following studies will be discussed in less detail than the prospective longitudinal studies described above.

A cross-sectional study of cognitive abilities and educational attainment in a population of school-age children from central Edinburgh, Scotland has been reported by Fulton et al. (1987) and Raab et al. (1989). The geometric mean blood lead level for the 501 children in the study sample was 11.5 µg/dl (range: 3.3-34.0). Multiple regression analyses indicated significant relationships between log-transformed blood lead levels and composite scores on the British Ability Scales ($p = 0.003$) and between blood lead levels and attainment test scores for quantitative ($p = 0.04$) and reading ($p = 0.001$) skills, even after allowing for 33 covariates. Grouping the subjects by blood lead levels showed a clear dose-response relationship without any evident threshold down to the lowest subgroup mean blood lead level of 5.6 µg/dl.

Hatzakis et al. (1987, 1989) conducted neuropsychological testing on 509 children living near a lead smelter in Lavrion, Greece, and found impairments in WISC-R IQ scores and reaction time performance scores. These effects were significantly associated with blood lead levels after controlling for as many as 23 covariates in multiple regression models. Blood lead concentrations ranged from 7.4 to 63.9 μg/dl and averaged 23.7 μg/dl. Depending on the number of covariates included in the model, full scale IQ decreased by 2.4-2.7 points for every 10-μg/dl increase in blood lead concentration. Subjects were grouped by blood lead levels (10-μg/dl increments) to analyze dose-response relationships for IQ as well as reaction performance scores. A nonlinearity in the dose-response pattern for IQ makes it difficult to interpret these data for a threshold. However, reaction time performance showed no evident threshold.

Wolf et al. (1987) used structural equation modeling to evaluate the variables related to low-level lead exposure and infant mental development in an urban population in Costa Rica. Blood lead levels averaged 10.8 μg/dl (range: 5.4-21.5 μg/dl) in 182 subjects whose average age was 16.6 months (range: 12-23 months). Blood lead had neither direct nor indirect effects on the Bayley MDI. However, blood lead did have a significant negative relationship with birth weight ($p = 0.05$) and mother's height ($p = 0.001$), as well as a positive relationship with mother's age ($p = 0.01$), after adjustment for covariates. Birth weight, iron deficiency anemia, and child's age had significant direct effects on MDI.

Vivoli et al. (1989) measured lead concentrations in blood, teeth, and hair, as well as ALA-D activity, in 237 children from Sassuolo, Italy. At the time of the study, blood lead levels averaged ~11.5 μg/dl. Although concurrent blood lead measures showed no significant relationship to covariate-adjusted scores on any of six neurobehavioral tests, tooth lead was significantly related to full scale and verbal WISC-R scores. Moreover, ALA-D was significantly associated with one verbal subtest of the WISC-R and with delayed reaction time performance.

Tooth lead also accounted for a significant amount of the variance in WISC-R full scale and verbal IQ as well as Bender Gestalt visual motor test performance in 156 children from Aarhus, Denmark (Hansen et al., 1989). Circumpupal tooth lead levels averaged 10.7 μg/g. A study of children in Brussels (Cluydts and Steenhout, 1989) showed marginally significant ($p < 0.10$) covariate-adjusted regression coefficients for tooth lead and neurobehavioral outcomes (WISC-R, reaction time and attentional performance), despite the small ($N = 41$) number of children evaluated.

In separate but similar studies conducted in Rhode Island and Lavrion, Greece, Faust and Brown (1987) and Benetou-Marantidou et al. (1988), respectively, administered neurobehavioral test batteries to small groups (N's of 15-30) of children whose blood lead levels had been measured at ~30-60 μg/dl. Significantly impaired performance was evident by comparison to matched controls, even after blood lead levels had been below 30 μg/dl for at least one year (Faust and Brown, 1987) or after a 4-year intervening period before follow-up testing (Benetou-Marantidou et al., 1988).

In analyses of data from the second National Health and Nutrition Examination Survey, Schwartz and Otto (1987) have also found evidence of retarded neurobehavioral development and impaired neurosensory capability in relation to low-level lead exposure. The ages at which a child first sat up, walked, and spoke were significantly associated with blood lead levels, as was also hearing threshold. The decline in hearing ability is qualitatively consistent with other evidence linking low-level lead exposure to electrophysiological changes in the auditory system (reviewed in U.S. EPA, 1986a).

With regard to fetal growth effects, a recent report by Ward et al. (1987) indicated that placental lead concentrations were highly significantly correlated with reductions in birth weight, head circumference, and placental weight in 100 obstretically normal births in England. Gestational age was correlated at borderline statistical significance ($p < 0.10$). Dividing the data into two birthweight groups, low (<3000 g) and high (>4000 g), revealed a highly significant difference in mean placental lead concentrations: 2.349 μg/g (S.D. = 0.883) versus 1.122 μg/g (S.D. = 0.361) for low and high weight groups, respectively. Of the 37 elements analyzed, lead and cadmium showed the most consistent negative relationships with these fetal outcomes. Other factors, such as parity, sex of neonate, social class, and history of miscarriage, did not appear to the authors to significantly confound their results.

Conclusions

As noted in the 1986 Addendum (U.S. EPA, 1986b), prospective studies offer a major advantage over cross-sectional and even many retrospective studies in that they provide a better history of lead exposure. This key difference is the reason why more weight is placed on findings from prospective studies.

However, notwithstanding this advantage, prospective studies may have various types of shortcomings in common with other epidemiological studies. One problem of particular importance is statistical power, especially in longitudinal studies that typically experience attrition and declining sample sizes over the course of the study.

The studies reviewed here differ considerably in population size and, even within some studies, in the number of subjects included in individual analyses. To illustrate, the first results from the Boston prospective study were based on analyses involving 201 infants out of a cohort of 249 (Bellinger et al., 1987a). By 5 years, the analyses were based on 170 children (Bellinger et al., 1989b). While this rate of attrition is certainly not high, it does nevertheless make it increasingly difficult to detect an effect of low-level lead exposure. According to Cohen (1977), an N of over 400 subjects would be required to detect an effect size of 0.01 with a power of 0.80 at an alpha of 0.05, one-sided. This calculation assumes that the analysis includes 13 covariates having an R^2 of 0.30. If the covariate R^2 is overestimated in the analysis for some reason, e.g., because of spurious sample correlations between covariates and blood lead or because the covariates are involved in causal pathways linking lead exposure to development, then regression methods may fail to detect a truly significant association between lead and developmental outcomes.

Another factor that can affect the power to detect a signficant relationship in these studies is the amount of variance in the sample blood lead measures. A small standard deviation in the independent variable (e.g., blood lead) will necessarily reduce any correlation between it and a dependent variable (e.g., MDI scores). Also, the presence of a significant effect of another variable on the outcomes under consideration will make it more difficult to detect the effect of lead exposure by regression analysis. For example, over 50 percent of the mothers enrolled in the Cleveland study were determined to be alcoholic, and significant early developmental effects were shown to be alcohol-related in the Cleveland study population (Ernhart et al., 1985b).

Perhaps the most surprising outcome of the prospective studies as a whole, then, is that so many of them are able to detect any effect of lead at all. Given the limitations of sample size and power of most of the studies under consideration, one's confidence in the reality of any detected effects that achieve statistical significance is enhanced. Conversely, it is difficult to interpret a failure to detect a lead effect as suggesting the absence of effect, if the analyses in question were based on fewer than 400 subjects, as was generally the case.

Despite these limitations, some important conclusions emerge from the findings reported above. Various lines of evidence still relate neurobehavioral effects to blood lead levels of "10-15 µg/dl, and possibly lower," as was previously concluded in the 1986 Addendum (U.S. EPA, 1986b). Further analyses from the Boston study, which has provided the most direct information bearing on dose-response relationships for neurobehavioral effects, not only supported the 10-15 µg/dl level of concern but indicated that MDI deficits can be detected in relation to cord blood lead levels of 6-7 µg/dl in lower SES children (Bellinger et al., 1988). Since the Boston cohort was mostly middle to upper-middle class, "lower" SES merely refers to less than the highest SES levels and is probably in fact much closer to the median of the U.S. population than the term suggests. Although the postnatal lead exposure levels were somewhat higher in the Port Pirie study, analyses of the relationship between postnatal blood lead levels and covariate-adjusted MDI scores provided "no evidence of a threshold effect" (Wigg et al., 1988). Indeed, restricting the analysis to children with blood lead levels below 25 µg/dl in the Port Pirie study yielded an even stronger association between covariate-adjusted McCarthy GCI scores and integrated postnatal blood lead measures (McMichael et al., 1988).

Supporting evidence for the stated level of concern may also be derived from other studies. Although McCarthy Scale results from the Boston study have not been analyzed in a manner to allow direct extraction of dose-response information, the average blood lead level significantly associated with covariate-adjusted performance on the McCarthy Scales (GCI and Perceptual-Performance subscale) was 6.8 µg/dl (SD = 6.3) (Bellinger et al., 1987b). Similarly, analyses relating cord blood lead levels to the G-R Neurological Soft Signs and, indirectly, to 12-month MDI scores were previously reported for the Cleveland study (Ernhart et al., 1986; Wolf et al., 1985), along with more recent significant results, by more than one analysis, relating cord blood lead to Length of Utterance, a measure of language development in 24-month-old infants (Morrow-Tlucak and Ernhart, 1987). Significant relationships were also indicated for maternal blood lead and deficits in 6-month MDI, PDI, and KID scores in the Cleveland cohort, but results of other analyses were mixed (Ernhart et al., 1987a). Any significant neurobehavioral effects associated with cord blood lead in the Cleveland study necessarily occurred at levels below 15 µg/dl since the maximum single cord blood lead level measured was only 14.7 µg/dl (mean: 5.99 µg/dl). Moreover, the fact that significant evidence of lead-associated impairments was found in a relatively small cohort (N's <200) suggests that the work was carefully conducted and that the results are credible.

Preliminary evidence from the Mexico City study is not inconsistent with a level of concern of 10-15 µg/dl, and possibly lower. Rothenberg et al. (1989) found that two measures of neonatal neurobehavioral function during the first 30 days of life were significantly accounted for by differentials in maternal blood lead levels during the last month of pregnancy and/or maternal and cord blood lead levels. The nature of the reported analyses does not provide direct dose-response information, but the mean cord blood lead level in the Mexico City cohort was 13.8 µg/dl and the mean maternal delivery blood lead was 15.4 µg/dl, levels that approximate the stated level of concern. However, little weight can be placed on these findings until more complete results are obtained from a larger number of subjects.

Some evidence from recent cross-sectional studies is also consistent with the identified level of concern. The Edinburgh study (e.g., Fulton et al., 1987) shows a significant relationship between blood lead levels averaging as low as 5.6 µg/dl and covariate-adjusted scores of cognitive ability and educational attainment. As noted by Grant and Davis (1989), this finding appears to closely parallel the results of Schroeder and Hawk (1987), whose North Carolina cross-sectional study population showed IQ deficits in relation to blood lead extending to levels as below 10 µg/dl. The latter study was described in detail and evaluated in the 1986 Air Quality Criteria for Lead (U.S. EPA, 1986a). In addition, the reaction time performance results of Hatzakis et al. (1989) showed no evident threshold over a blood lead range of 7.4 to 63.9 µg/dl.

Based on all of the above considerations, a blood lead concentration of 10-15 µg/dl, and possibly lower, remains the level of concern for impaired neurobehavioral development in infants and children. Given the fact that such effects have been associated with blood lead measures in pregnant women, umbilical cords, and infants up to at least 2 years of age, there is no apparent distinction at present as to whether this level of concern applies to only fetuses or infants or preschool-age children. Thus, a blood lead level of 10-15 µg/dl, and possibly lower, ought to be avoided in pregnant women, fetuses, infants, and young children, although it is recognized that pregnant women per se are not necessarily a population at risk.

Various lines of evidence suggest that lower SES and male gender are additional risk factors for the developmental effects of low-level lead exposure. Increased vulnerability in lower SES children has been indicated in analyses of MDI scores (Bellinger et al., 1988) and MDI-GCI change scores in the Boston study (Bellinger et al., 1989b) and in the MDI results from Cincinnati (Dietrich et al., 1987b, 1989b). Also, some IQ results from cross-sectional investigations are consistent with the view that lower SES children are more vulnerable to lead-induced cognitive impairment (Harvey et al., 1984; Lansdown et al., 1986; Schroeder and Hawk, 1987). Greater susceptibility of male infants to lead developmental toxicity has been evident in analyses of MDI-GCI change scores in the Boston study (Bellinger et al., 1989b), in MDI results from the Cincinnati study (Dietrich et al., 1987b, 1989b), in reanalyses of IQ data from the Southampton cross-sectional study (Pocock et al., 1987), and in some early data on sex ratios of stillbirths in Port Pirie and other locations (Scragg et al., 1977).

The evidence regarding pregnancy outcomes and physical growth effects related to prenatal lead exposure is less consistent than that for neurobehavioral outcomes. Such was the case at the time of the 1986 Addendum (U.S. EPA, 1986b) and is still the case simply because little additional information pertaining to pregnancy outcomes and growth has appeared since the 1986 assessment.

As far as growth effects are concerned, the Cincinnati study has shown a significant covariate-adjusted reduction in birth weight associated with prenatal (maternal) blood lead levels (Bornschein et al., 1989). In addition, early postnatal (3-15 months) growth rates have also been associated with lead exposure pre- and postnatally in the Cincinnati study (Shukla et al., 1987). (Interactions with other variables were evident in both of these cases, which will be discussed further below.)

Some supporting evidence of lead-related reductions in birth weight also comes from the Boston and Mexico City studies and, possibly, the Glasgow study. Although birth weight per se showed no relationship to cord blood lead in the

Boston study, there was an exposure-related trend in the percentage of small-for-gestational age infants that approached statistical significance (Bellinger et al., 1984a). In Mexico City, the difference in the blood lead level of the mother at 36 weeks versus either her level at delivery (M36-MD) or the blood lead level of the cord (M36-UC) accounted for a significant amount of the variance in birth weight (Rothenberg et al., 1989). Similar findings ($p \cong 0.06$) were noted for chest circumference and trunk length. In Glasgow, the high maternal blood lead group (mean: 33.05 µg/dl) weighed 3.32 kg, on average, at birth, whereas the medium blood lead group (mean: 17.73 µg/dl) weighed 3.43 kg and the low group (mean: 7.02 µg/dl) weighed 3.51 kg (Moore et al., 1989). However, these data were not adjusted for covariates and were not tested for statistical significance.

Otherwise, no other prospective study has shown a significant association between reduced birth weight and lead exposure. The Yugoslavian study (Graziano et al., 1989b), in particular, has failed thus far to yield any evidence of lead-related birthweight reductions in more than 900 births, even at relatively high blood lead levels. Also, analyses by Ernhart et al. (1986) showed no significant effect of lead on birth weight, birth length, or head circumference; nor, according to preliminary analyses, was any effect evident on postnatal growth (Marler and Ernhart, 1987). However, the cross-sectional analysis by Ward et al. (1987) did indicate highly significant simple relationships between placental lead concentrations and reduced birth weight and head circumference.

The Port Pirie study provided strong evidence relating prenatal lead exposure to increased risk of preterm delivery (<37 weeks gestation) in a sample of 749 pregnancies (McMichael et al., 1986). Also, a small but significant relationship between prenatal lead and gestational maturity was observed in the structural analyses of the Cincinnati study (e.g., Dietrich et al., 1987b). However, regression analyses of a different sample from the Cincinnati study did not reveal a significant association between prenatal lead and preterm (<35 weeks) deliveries (Bornschein et al., 1989). Also, as previously discussed in the 1986 Addendum, the Boston prospective study showed a positive but nonsignificant relationship between cord blood lead and gestation length (Bellinger et al., 1984a), whereas the cross-sectional study of Moore et al. (1982a) found signficant negative associations between gestational age and maternal as well as cord blood lead after allowing for a number of covariates.

Placental lead concentrations appeared to be inversely related to gestation length in the analyses of Vimpani et al. (1989) and Ward et al. (1987), but were of uncertain statistical significance.

There are many possible explanations for these apparent inconsistencies among studies. The lack of a significant difference in pregnancy outcomes between the high exposure and reference communities in Yugoslavia (Graziano et al., 1989a,b) could reflect the difficulty of assessing fetal lead exposure by means of maternal blood lead levels. With regard to gestation length, Bornschein et al. (1989) noted that their analysis was restricted to pregnancies of at least 35 weeks. A similar cutoff of 34 weeks was used in the Boston prospective study (Bellinger et al., 1984a). Constraining the data in this fashion could make it more difficult to detect an effect on gestation. Also, there were interactions involving mother's age and race evident in the Cincinnati study (Bornschein et al., 1989). Thus, differences in the age of the mothers, racial make-up, other population characteristics, sample sizes, level of lead exposure (current as well as past), and approaches to analyzing data could underlie the varying results of different studies.

Based on the evidence reviewed here and in the 1986 Air Quality Criteria for Lead (U.S. EPA, 1986a), it seems likely that prenatal lead exposure poses a potential hazard to the developing fetus in terms of reduced gestational length and possibly other aspects of fetal growth (in addition to postnatal neurobehavioral development, as already noted above). It is difficult, however, to derive a definitive dose-response relationship for fetal outcomes from the available data, although some indications point to a level of concern starting in the region of 10-15 µg/dl. The average maternal blood lead levels in the studies where the pre-term delivery effect was clearest (Port Pirie and Glasgow) was in the 10-15 µg/dl range, with somewhat mixed findings in the Cincinnati, Boston, and Cleveland studies where the maternal or cord blood lead levels averaged below 10 µg/dl. A similar pattern seems to hold for birth weight as well. The strongest evidence of a birthweight effect comes from the Cincinnati study, with some of their analyses suggesting that such an effect could start in the region of 12-13 µg/dl, but possibly extending from 7 to 18 µg/dl. However, other prospective studies provide no support for this conclusion, and so it must be considered an open issue for more definitive resolution.

The issue of the persistence of the neurobehavioral effects needs to be considered in an assessment of the risk of low-level lead exposure. If decreased scores on the Bayley Scales reflected merely a transient delay in children's neurobehavioral development -- a minor perturbation that children could quickly "grow out of" -- then the public health significance of lead exposure at blood lead levels of 10-15 μg/dl would perhaps be diminished. Some recent results from two of the studies that had convincingly demonstrated a link between prenatal lead exposure (either maternal or cord blood lead levels) and early deficits on the Bayley Mental Development Index now suggest that the association between prenatal lead exposure and cognitive development may not hold up at later ages. The Cincinnati study found a declining influence of prenatal exposure indicators on MDI scores at 12 months and 24 months: only 10-day blood lead measures were significantly associated with MDI scores at 12 months, and no significant negative PbB-MDI relationships were evident at 24 months (Dietrich et al., 1989b). Although the Boston study did continue to find a significant relationship between prenatal lead exposure (cord blood lead) and MDI performance at 24 months, no relationship could be shown for prenatal lead exposure and cognitive abilities at 57 months on the McCarthy Scales (Bellinger et al., 1987b). Thus, one implication of these findings might be that the effects of prenatal lead exposure on neurobehavioral development are not permanent.

Such a conclusion could be valid, but the evidence available to support it is not adequate. The inability to detect a continuing significant association between prenatal lead exposure and neurobehavioral function at age 2 in the Cincinnati study or age 5 in the Boston study could result from, among other things, a lack of adequate statistical power, as noted above. Other factors could also interfere with detecting such a relationship and possibly account for differing results in separate studies. For example, it is not clear which measure of blood lead provides the best indicator of exposure during critical periods of organogenesis. The Cincinnati study primarily used maternal blood samples obtained during the first or second trimester of pregnancy to indicate prenatal lead exposure. Prenatal exposure was also reflected in samples taken from the Cincinnati infants 10 days after birth (gestationally corrected), but comparatively few cord blood samples were available for data analyses. The Boston study relied exclusively on cord blood samples while other studies have also sampled the mother's blood around the time of delivery. As suggested previously (U.S. EPA, 1986b; Davis and Svendsgaard, 1987) and supported by preliminary results from the Mexico City study (Rothenberg et al., 1989), there may be differences in these measures, particularly during the last month or so of pregnancy, that reflect important biokinetic transfers of lead between compartments, both within the mother and infant individually and between them.

In addition to the nature and extent of such biokinetic transfers, their timing (and the point at which blood lead is sampled) could make an important difference in the ontogenesis of neural structures and, consequently, later neurobehavioral function. It is interesting to note, for example, that almost no significant negative associations have been found, after covariate adjustment, between concurrent blood lead levels and postnatal outcomes in any of the prospective studies reviewed here. Rather, cumulative past exposure (e.g., average postnatal blood lead levels) or, in several instances, blood lead levels several months or years prior to a given outcome have shown the strongest relationship to postnatal neurobehavioral effects. Such a lagged effect has been suggested by several findings, as shown in Table 13. When significant positive (unpredicted) relationships between a measure of blood lead and some outcome have occasionally been found, they generally involved concurrent blood lead levels.

Thus, it may well be that the ability to detect a significant relationship between low-level lead exposure and neurobehavioral outcomes depends, at least in part, on where and when the measure of blood lead is obtained. Since the fetus and infant constitute the population at greatest risk, it would be preferable to measure a direct indicator of their exposure. However, that approach has not been as feasible as measuring a related indicator, such as maternal or cord blood lead. (Even cord blood is sampled from the placental rather than the fetal side and may therefore not fully reflect fetal exposure.) Consequently, measures such as maternal and cord blood lead levels, while reasonably good indicators of prenatal lead exposure, may not afford the most accurate predictors of later neurobehavioral outcomes.

Another factor that could obscure a relationship between prenatal lead exposure and postnatal neurobehavioral function and that could account for some differences in results among studies is the rather precipitous increase in lead exposure observed in most of the prospective studies during the first 2-3 years of life. Sizeable rises in postnatal blood lead levels were noted in the Cincinnati, Cleveland, and Port Pirie studies, but not in the Boston study.

TABLE 13. STRONGEST RELATIONSHIPS BETWEEN BLOOD LEAD MEASURES AT SPECIFIED TIMES AND LATER NEUROBEHAVIORAL OUTCOMES AS DETECTED BY PROSPECTIVE STUDIES

Study	Time/Type of Blood Lead Measure	Outcome
Boston (Bellinger et al., 1987a,b)	Delivery/cord	6- , 12-, 18-, and 24-month MDI
	2 yr	5-yr McCarthy
Cincinnati (Dietrich et al., 1987b, 1988; Bhattacharya et al., 1988, 1989)	Prenatal ($\bar{X}$: 16 wk)/maternal	3- and 6-month MDI
	10 day	12-month MDI
	2 yr	6-yr postural sway
Cleveland (Ernhart et al., 1986, 1987a; Wolf et al., 1985; Morrow-Tlucak & Ernhart, 1987)	Delivery/cord	12-month MDI (via 30-day G-R soft signs)
	Delivery/maternal	6-month MDI, PDI, KID
	Delivery/cord	2-yr language acquisition (2 measures)
Pt. Pirie (Wigg et al., 1988; McMichael et al., 1988)	6 month	2-yr MDI
	6, 24, 36 month and integrated postnatal	4-yr McCarthy
Sydney (Cooney et al., 1989b)	Cumulative (prior plus current)	36 to 48 month change in cognitive development (p = 0.14, two-tailed)

None of the first three studies showed a significant association between prenatal lead exposure indicators and 2-year MDI scores, but the Boston study did. While analyses from the Boston study also indicated that continuing "high" lead exposure (>10 μg/dl) contributed to a persistence of neurobehavioral deficits at later ages, a high postnatal blood lead in the Boston cohort was not as high as the average for any of the other prospective studies at age 2 years. Thus, the relationship between lead exposure at a critical stage of early development and subsequent neurobehavioral function could be obscured by differential lead exposure (most often, but not always, increased exposure) in the intervening period.

By this line of reasoning, one would perhaps expect that increased postnatal PbB measures should then show a significant relationship to later neurobehavioral outcomes. This was in fact the case in the Port Pirie study, where sample size was more clearly large enough to afford relatively good statistical power. (This also points up, as discussed above, why it is not possible at present to discriminate between prenatal and postnatal lead exposure in stating a blood lead level of concern for developmental neurobehavioral effects.)

It should also be kept in mind that scores on tests such as the Bayley or McCarthy Scales are only indicators or reflections of neurobehavioral function. Such variables may be valid and reliable mesures, but they do not fully represent all aspects of a child's cognitive, social, and emotional development. Thus, considerable caution must be exercised in drawing conclusions from findings of "no effect." Not only are there many facets to a child's development that need to be assessed, but these facets may interact in complex ways that may be quite difficult to detect or evaluate. For example, a child's emotional and social adaptation (including such notions as "self-esteem") may be influenced in subtle as well as obvious ways by his or her cognitive abilities.

Such complexities make it difficult to presume that a failure to detect a continuing association between an indicator of prenatal lead exposure and, for example, scores on the McCarthy Scales at 5 years is evidence of no permanent effect. It is well known that the nervous system is capable of adapting to and even compensating for various insults during early development. But it is also true that the full realization of developmental potential can very much depend on events during critical stages of ontogeny. A parallel may be drawn with impaired language acquisition in children whose hearing has been affected by chronic otitis media (e.g., Kavanagh, 1986). Although otitis media itself may be transient and fully reversible, it secondary effects on language development in young children may be much longer lived. As noted by Jenkins (1986, p. 216), "With a fluctuating hearing loss, such children may receive inconsistent and inadequate information, or may have to devote so much attention to the decoding process itself that there is little capacity left over for higher-order cognitive operations. If children are, in fact, doing something different or expending more resources on lower levels of speech perception, we may see deficits in other processes at a later period."

It is also important to note the convergence of animal findings, particularly those showing impairments in higher-level behavioral processes such as discrimination reversal learning in primates as well as rodents at blood lead levels below 20 µg/dl. A number of such studies, conducted in at least three independent laboratories, provide evidence free of the socioeconomic and other complex variables that sometimes complicate the interpretation of the human literature. These studies were summarized and reviewed in Air Quality Criteria for Lead (U.S. EPA, 1986a).

A remaining issue is whether the effects discussed here are large enough to constitute a significant risk to public health. Valuable information has been provided by various prospective studies on the magnitude of neurobehavioral deficits relative to increments in blood lead levels. Despite different approaches to treating their data, three of the prospective studies provide results suggesting that Bayley MDI scores decline by 2-8 points for approximately every 10-µg/dl increase in blood lead level. The Boston study found 4-8 point differences in 6- to 24-month MDI scores between high (mean: 14.6 µg/dl) and low (mean: 1.8 µg/dl) cord blood lead groups. The Cincinnati study showed as much as an 8.4-point decline in boys 6-month MDI scores for every 10-µg/dl increment in maternal blood lead. Also, the Port Pirie study demonstrated a 1.6-point decrease in the 24-month MDI per 10 µg/dl of blood lead at 6 months, and a ~3.5-point decrease in GCI scores for every 10 µg/dl in average postnatal blood lead. As noted by Davis and Svendsgaard (1987), an overall 4-point downward shift in a normal distribution of scores such as the MDI or GCI would result in 50 percent more children scoring below 80 on these exams (cf. Needleman, 1983; McMichael et al., 1988).

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